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BRITISH MEDICAL JOURNAL

LONDON SATURDAY DECEMBER 24 1960

THE CHALLENGE TO THE MEDICAL PROFESSION*

BY

Sir FRANCIS R. FRASER, M.D., LL.D., F.R.C.P., F.R.C.P.Ed.

To be invited to deliver the Harveian Oration is one of the highest honours which you can bestow on a colleague, and I am conscious of the importance of the occasion and of my inadequacy to do it justice. To commemorate all the Benefactors of our College who have added to its material and intellectual wealth over a period of three centuries is an impossible task. To exhort the Fellows and Members to search out the secrets of Nature and to continue in mutual love and affection is also the duty of the Orator, and it is to this more general instruction that I propose to devote the time at my disposal.

Each Orator must to a large extent reflect his own experiences and interests during his professional career, and the 50 years since I graduated in medicine have seen changes in the ability of each medical practitioner to relieve the sufferings of his fellow men, and changes also in the community which it is his privilege to serve —changes that are indeed remarkable and perhaps unprecedented in any previous half-century. These changes are still proceeding actively, and no one can foresee what lies before us and our successors; but it has been a privilege to observe the trend of events during such an exciting period. The study of man is but a part of biological science, but, while the behaviour of other animals seems to be governed by the urge for survival of the species, man has shown a capacity to create conditions which direct his behaviour in unforeseeable ways. From this, new situations arise to which the individual is able to adapt with varying degrees of success, and with ever-changing effects upon his health and happiness.

Harvey's Influence on Biology

Since I accepted the invitation to deliver this Oration, I have been spurred to reread and, in some instances, to read for the first time, the published works of William Harvey and also many of the volumes, chapters, and articles that have discussed the importance of his work, the ideas existing at the time that may have influenced him, the type of man he was, and the results of his great discovery of the circulation of the blood. I have read also a considerable number of the Orations of my predecessors and numerous publications of recent years that might have a bearing on the relations of our profession to the community which we serve. None of these studies has affected me as did the film produced in 1928 for our College by Sir Henry Dale and Sir Thomas Lewis. That seemed to me to demonstrate, as no translation of *De Motu Cordis* before or since has done, the essence of the scientific method and also the perseverance and patience required to establish a truth —"To search and study out the secrets of Nature by way of experiment."

William Harvey was a physician and an ornament of our College, and it is natural that most of the literature dealing with his discovery of the circulation stresses the influence of his work on the practice of medicine; but when first I read *De Motu Cordis*, when I saw the film here in 1928, and in my reading during the past year, it has been the much wider influence that has impressed me—that on the science of biology. In this larger field of knowledge, which includes, of course, the lesser field of medicine, it has been well said by Charles Singer (1950) that "Harvey was the first to give a really adequate explanation, in physical terms, of any bodily process. From Harvey's time to our own the interpretation of bodily activities in terms of physics and chemistry has been one of the main tasks to which biologists have set themselves. Harvey's work is thus not only the starting-point of the modern science of physiology but it is also the first milestone on the road to the modern rationalization of biological thought." And again the same author has written: "The blood, it was seen, is a carrier going round and round on the same beat. What it carries, and why, how and where it takes up its loads, and how, where, and why it parts with them, these are questions the answering of which has been the main task of Physiology in the centuries that have followed."

The tercentenary in 1957 of Harvey's death produced many articles of interest and importance. One that impressed me particularly as stressing the general biological range of Harvey's genius is that by Professor F. J. Cole (1957), who states that in Harvey's published works he cites observations on 128 types of animal life, and in *De Motu Cordis* alone there are observations on 49. His work is regarded by many authors as marking the ending of the myths and conjectures that governed man's thoughts on the relation of life to the world around him. It was a particular instance of the scientific advances then taking place in the sciences, in astronomy, physics, chemistry, and anatomy, but it was many years before it was to exert any influence on the practice of medicine.

What Harvey did was to show that biological problems could be solved by the methods of observation, experiment, and measurement; but more than two centuries were to pass before these methods were to be applied extensively to the solution of the many

*The Harveian Oration, delivered at the Royal College of Physicians of London on October 18, 1960.

problems facing the clinician in the understanding of disease and in the treatment of patients. In the intervening years many important advances were made in anatomy, physiology, pharmacology, morbid anatomy, bacteriology, and hygiene, but the methods that were devised for the advance of these subjects were not applied to the problems of clinical medicine. There were not the opportunities to do so. The clinician did not have the laboratory facilities nor the skills required, even if he appreciated how these methods might assist him. By the end of last century the teaching hospitals of this country were mostly provided with pathological laboratories, and the physicians and surgeons could get reports on the histology and bacteriology of specimens obtained from their patients, and on the results of the simpler chemical tests; but clinical science and research as we now know it did not exist.

Development of Clinical Science

In an address at Oxford on the evolution and organization of the university clinic, Dr. Simon Flexner (1939) stated that the first clinic of this kind was that at Munich under Von Ziemssen, where in 1878 laboratories were provided in close relation to the clinic "in which advanced students and assistants study primarily problems of disease derived from the patients, but it does not exclude the study of more fundamental scientific subjects." There were considerable objections to the plan, such as that students would be made too scientific, an idea that is still familiar. This was followed in 1892 by a clinic at Leipzig under Curschmann, and later at other centres in Germany. In 1895 the first centre of this kind in the United States of America was established at the University of Pennsylvania when the William Pepper Laboratory of Clinical Medicine was attached to the wards of the hospital, to be followed 10 years later by the Hunterian Laboratory for research in surgery under Halsted at Johns Hopkins Hospital in Baltimore and in 1906 similar laboratories for the Department of Medicine there under Barker.

We owe the provision of comparable opportunities in this country for seeking out the truth in the clinical subjects to the Royal Commission on University Education in London (the Haldane Commission) which was appointed in 1911 and issued its final report in 1914, just before the outbreak of the first world war. The Commission heard evidence from representatives of all the medical schools in London, but what was of more importance in leading the Commission to its conclusions was the evidence given by Professor Von Müller, of Munich, Mr. Abraham Flexner, Sir William Osler, and Professor Starling. Before giving evidence the representatives of the schools had received a memorandum contributed by Abraham Flexner which included the following:

"Clinical teaching in London remains an incident in the life of a busy consultant who comes to his post through promotion on the basis of seniority, and visits his too miscellaneous wards twice weekly in the afternoons between, perhaps, two and four, in company with his house-physician and clinical clerks. There is no certain or direct interaction between the fundamental scientists and the clinicians; except in the region of morbid anatomy, some elementary bacteriology and physiological chemistry, they barely touch. The clinician lacks the time even if he has had the training, which will enable him to bring to bear upon clinical problems the artillery which chemist and pharmacologist are forging. Nor are the teaching hospitals equipped and organized with a view to teaching of University quality. They are admirably designed and conducted for the care of the sick on a routine basis. But their laboratories need to be greatly extended and their staffs completely reorganized before they can serve as University Hospitals."

And it continued:

"In order to reconstruct a London Medical School on modern lines, it would be necessary completely to reconstitute the staff, to break up the present method of appointments by seniority, to salary teachers of medicine in order that they may devote their main time and thought to teaching and investigation, to introduce increased differentiation of material and to add to the existing hospital wards laboratory equipment along the lines in which the clinician is interested in working. It must be made possible to import into London the scientific producing clinician—devoted to teaching and research—from any place in which he may be found; and younger men must be taught that their chances of higher appointments depend, not on using themselves up in tutorial coaching, not on faithfully stepping into the breach when the superior is absent nor following in his footsteps when he is present, but on the development of their own powers along genuinely productive lines."

The reactions of the representatives of the medical schools to these criticisms and suggestions make interesting reading. Some of them, notably Henry Head, Archibald Garrod, and Sir Bertrand Dawson, as they then were, accepted the criticisms and also, with modifications in detail, the suggested reforms. But many of the others maintained that the existing methods of staffing the hospitals and of teaching produced such good results in the advancement of knowledge of practical clinical medicine and in the training of students to become good doctors that there was no need for change. Now, 50 years later, these views are still held, but by a dwindling number of physicians and surgeons.

The section in the final report of the Commission that deals with medical education in London is a long one and I must be content to quote a few paragraphs only from it, those that seem to be relevant to William Harvey's instruction to us to seek the truth and those that encourage us to follow his example of accurate observation and experiment. Before the conclusions are reached the following paragraphs occur:

"Under the existing system, the students are taught the practice of the applied science of medicine, or as it may be called, the art of medicine, better than under any other—the art of examining a patient and gathering from his symptoms and physical and mental conditions, with all the aids which scientific procedures can give, an accurate diagnosis of the case. Under this kind of clinical teaching the student serves an apprenticeship, and actually acquires, in the course of his instruction at the hands of experienced physicians and surgeons, the training and experience which fit him for the practice of his profession. No one suggests that this method of teaching should be abandoned or superseded."

And:

"But what is suggested and insisted on is that if, as is admitted, co-operation is necessary for the practice of medicine at the level of medical science to-day, it is also necessary, even in a higher degree, for the advancement of medical science beyond its present stage; further, that this co-operation does not exist in the Hospital Medical School, and cannot do so as long as the physicians and surgeons make use of science only to aid them in recognizing and curing disease, and in teaching the students to do so on the basis of existing knowledge. It is maintained that they must give their time to attacking the problems of disease, and that they do not do so alone, but must become members, and controlling and directing members, of a group

of men working together for a common end—a group in which the subordinate members are selected with a view to the special knowledge required to aid and supplement that of the leading and directing mind. They must devote themselves to original research under the conditions which make it productive in the case of the exceedingly complex problems which medical science has to solve. Finally, it is said that the 'hospital unit' is the kind of organization which experience has already shown provides the conditions required; and that it is only when the conditions have been found and established which make research in medical science possible and actual that the true University spirit will inform the teaching, and that the teachers will be the kind of men we have spoken of as University Professors—men who will do for medicine what other men do for physiology and chemistry, and, indeed, for every subject which is capable of being scientifically treated."

Finally, the Commission came to the following general conclusions:

"1. The standard of the teachers in these [the clinical] subjects ought not to be different from that of University Professors in other subjects, and it is therefore necessary to appoint and pay professors of the various branches of clinical medicine and surgery who will devote the greater part of their time to teaching and research.

"2. The complex nature of the science of medicine and its dependence for assistance on other branches of science necessitate co-operation, and the special organization of a professorial department, in order to enable the professor to carry on research successfully, and also to give scientific instruction in the subject.

"3. The kind of organization known as 'The hospital unit' appears to be well fitted for attaining this end. It consists of: a professor with the control of wards; an out-patient department; assistants nominated by the professor with a view to complementing his own knowledge and affording him the special assistance he requires to carry on research in the direction in which he is interested; and finally, laboratory accommodation in close proximity to the wards, not only for the service of the wards and the examinations and procedures connected with the diagnosis and treatment of the cases, but also for the purpose of research."

Establishment of Clinical Units

With the outbreak of the first world war in 1914 no immediate action was taken as a result of this report. In 1919, however, the Board of Education offered grants to the medical schools in London to enable them to establish clinical units, each to be "under the control of a whole-time director, to have adequate beds, assistants and laboratory facilities." Near the end of 1919 the responsibility for giving grants to universities was transferred to the newly formed University Grants Committee, which required that the directors of the units should, if possible, be appointed professors by the University. There were difficulties in providing the necessary laboratory facilities adjacent to wards, but with the help of grants from outside sources these were overcome and professorial units were established. By the end of 1921 there were in London five units in medicine and four in surgery under the direction of either full-time university professors or part-time directors, and one unit in obstetrics and gynaecology had been approved by the University but no chair was instituted until some years later. The Haldane Commission was appointed to advise on the University of London, and its recommendations on medical education applied to the medical schools of London only, so that it is not surprising that the schools of universities outside London did not adopt the suggestion of "clinical units" at that time; but there was one exception, for the Medical School in Cardiff established units in medicine and in surgery in 1921 with full-time professors in charge of them.

The recent war (1914–8) and the importance of conserving manpower had impressed on physicians and surgeons the need in peacetime also for more accurate methods of diagnosis and controlled methods of treatment. They were eager as never before to make use of any help they could get from physiologists and biochemists and their quantitative methods. Thyroid surgery, for example, was being developed, and the need for measurements of the basic metabolic rate for the assessment of thyroid function was recognized. The occasional occurrence of parathyroid tetany aroused interest in both hypoparathyroidism and hyperparathyroidism and the need for calcium balances to control treatment. Of perhaps even more importance was the discovery by Banting and Best of insulin, and the need this created for quantitative methods of estimating acid-base relationships, for blood-sugar curves, and so on. It was members of the staffs of the professorial units who carried out these procedures in those early days. The units in London were thus established just in time to meet this challenge to clinical medicine of important advances in the basic sciences. I remember well how one of my colleagues suggested that we were in danger of forgetting to look for specific aetiologies in our enthusiasm for elucidating physiological distortions. I would suggest, however, that the establishment of these clinical units was the first concerted action in this country to enable clinical medicine to meet the challenge of William Harvey's great achievement by training young clinicians to be clinical scientists.

In an address delivered just a year ago, Sir Lindor Brown (1960) said: "The physician no longer needs the physiologist to visit his wards and explain to him some of the finer points of recent discoveries in cardiovascular physiology, or gaseous exchange in the lungs, or of renal function. The boot is very much upon the other foot. The cardiologist now makes measurements on man that the conventional physiologist of the past had never dreamed of, progress in the respiratory physiology of man comes from the ward rather than the laboratory, and the activities of diseases effect such spectacular changes in the balance of food and electrolyte that they far outdo anything that the most enterprising experimenter can produce in the laboratory. The effect of all this is to make the physiologist less necessary in the wards and the physician more necessary in the laboratory."

The Goodenough Report

There was little further development between the two world wars except for the appointment of a full-time professor of medicine at Bristol in 1935 and the establishment of the Postgraduate Medical School of London at Hammersmith Hospital. There the professors of medicine, of surgery, and of obstetrics and gynaecology are not the directors of units within the School and Hospital but are responsible for the care of the patients as well as for the teaching and research in the whole of the departments in their subjects. This was the arrangement favoured by the Haldane Commission but not regarded as practicable for the London undergraduate schools and hospitals at the time of the Commission's Report.

In 1942 the Inter-Departmental Committee on Medical Schools—commonly known as the Goodenough

Committee—was appointed, and reported in 1944. At that time the second world war was drawing to a close and medical education and the hospital services had been altered drastically to meet the needs of the war so that there appeared to be peculiar opportunities for adjustment and improvement with the reorganization that would be necessary. The voluntary system of hospital finance had broken down and a National Health Service was being planned. The Committee's reference was "To inquire into the organization of medical schools, particularly in regard to facilities for clinical teaching and research."

The Report is a long one, and in many respects continues and carries on from the recommendations of the Haldane Commission. The General Summary of the Report contains the following:

"In harmony with the general body of evidence it is recommended that at the earliest possible date the staff of every medical school should include a whole-time professor in each of the departments of general medicine, general surgery, and obstetrics and gynaecology. This goal may have to be reached by stages as suitable men and women become available. . . .

"All clinical departments should have a number of whole-time appointments in the intermediate and junior grades, particularly the latter . . .

"Medical schools, teaching hospitals and postgraduate institutes have three important functions in relation to medical research: (i) to discover and train future research workers; (ii) to encourage and facilitate original investigations by members of their teaching staffs; and (iii) to house special research units and workers."

These recommendations have been carried out to an extent that is remarkable in the few years that have elapsed. There are now only a few medical schools without a full-time professor of medicine as director of a unit with full-time assistants, wards, and laboratories. There are more so far without a similar unit in general surgery, and there are as yet only a few such units in obstetrics and gynaecology. It is extremely gratifying to see the large number of young clinicians now in this country, trained to utilize the methods of the basic sciences for the elucidation of the problems met in patients and capable of adapting them and of devising new ones to meet the peculiar conditions of clinical medicine. There can be little doubt, I think, that this is the result of the establishment of the "clinical units" directed by persons appointed by the universities, and with conditions of appointment similar to those of professorships in other university subjects and to the influence of these units on the standard of work of all our hospitals.

Changing Conditions of Medical Practice

There is to me one striking difference between the reports of the Haldane Commission and of the Goodenough Committee. The former discusses briefly the need for the instruction of undergraduates in lunacy and mental diseases, and considers that this could be carried out in special institutions; the Goodenough Committee, in contrast, discusses at some length and in considerable detail the teaching of social and preventive medicine and of psychiatry, and advises that there should be special departments in the teaching hospitals in which undergraduates can be taught and experience the importance of these subjects in the practice of medicine. This difference in the space of 30 years reflects a change in the conditions of medical practice that had taken place between the wars and that has continued at an increasing rate during the years since the end of the second world war.

A graduate of the period before the first world war could not fail to be impressed by the significance of the work of such men as Pasteur, Koch, Lister, and Manson, and of the great benefit to mankind that could result from the discovery of the specific causes of diseases, and which would, it was hoped, be followed by specific treatment by means of antisera, as shown by von Behring for diphtheria, or prevented by vaccines through the work of Almroth Wright, while specific chemotherapy was on the horizon through the work of Ehrlich. It seemed as if all that was necessary was to find the specific cause, be it bacterial or protozoal, and methods of diagnosis, treatment, and prevention of disease would follow. However, the growing appreciation in the following years of the effects of deficiency and of excess of the secretions of the internal secreting glands, and of the essential accessory food factors, for example, emphasized the relative nature of health and ill-health, and the experience of the first world war had not only confirmed this but had also demonstrated the importance of mental and emotional factors, and directed interest to a wider concept of psychiatry than that generally accepted at the beginning of the century. At the same time it was recognized that these minor mental or emotional disturbances were frequently the result of conditions in the home or at work, and often due to the personal relations with other members of the family, with neighbours, or with colleagues at the place of employment. Thus it is often difficult to distinguish between the fields of social and preventive medicine and of psychiatry.

Most medical schools now have departments of psychiatry and a few have departments of social medicine, but there are still not nearly enough men with the appropriate training and experience to be in charge of academic departments in social medicine. The departments that have been established are busily engaged in research. In social medicine this is usually concerned with the correlation of housing, industrial conditions, density of population, etc., with morbidity, and requires statistical treatment. In psychiatry the major mental disorders are being investigated by physiological, biochemical, pathological, and experimental methods, but there is so far little if any basic knowledge of how emotional and mental disturbances affect physiological processes and still less how they are able to contribute to the incidence of structural changes. And there are also the reverse problems of the effects of illness on the social equilibrium of patients and their families, and on their mental and emotional reactions.

Without doubt we will, before long, understand the disturbances to health and happiness due to these factors much better than we do now. As Lord Adrian (1959) said in his address to the meeting in Edinburgh of the British Medical Association: "We must learn more about the effect of social pressures, the particular conditions in our own ways of life and in human society generally which lead to anxiety or psychosis." And he continued: "Social science and its applications to medicine may have been poorly served by the enthusiasts, and some of their conclusions have been criticized as vehemently as we were once accustomed to criticize Freud." He concluded his address by saying: "We need not worry too much at having found no answer to an old philosophical dilemma, but we have patients with troubles to be prevented or put right, and we have

learnt to respect troubles that we used to neglect. . . . We still have a long way to go before we can claim any striking advance. But it is our privilege as well as our responsibility to work for it, and it will be a work in which every one of us can share."

Effect of the National Health Service

Shortly after the publication of the report of the Goodenough Committee the National Health Service was established with its three main divisions of local authority, hospital, and general practitioner services, and the Ministry of Health invited universities with medical schools to accept responsibility for providing postgraduate or continuing education for the general practitioners in the region in which each university is situated. In this way my colleagues and I have become conscious of the large proportion of the work of general practitioners concerned with illnesses in which social and mental conditions appear to be important or even the dominant factors, and in the years since the second world war there have been numerous publications confirming this and maintaining that there has been an actual increase in the number of patients suffering from such conditions. It is difficult to find any satisfactory evidence of such an increase, but there is no doubt of the increase in the number of patients applying for help in whom these factors rather than organic diseases appear to their doctors to be important.

It is easy to suggest possible reasons for an absolute increase. These vary from lack of the support of religious beliefs to mechanization of industry, from the loosening of family and community loyalties to urbanization and the new towns, and from the boredom of life under the Welfare State to dependence on newspapers, television, wireless, and the cinema for ethical and moral values and codes of behaviour. It is generally agreed that it is the rapidity of change in these social conditions to which many individuals are unable to adjust that is the important factor. On the other hand, with the remarkable strides that have been made in clinical science during the past 50 years, the clinician is now able to obtain quantitative assessments of deviations from the normal in numerous physiological, biochemical, and biophysical functions, and to use these as guides to treatment. As a result there has undoubtedly been a temptation to concentrate attention on these abnormalities that can be measured and to ignore the numerous others that cannot. Be that as it may, few generalizations or principles that can be taught to undergraduates or postgraduates to guide them in their care of individual patients have been established in the fields of social medicine and psychiatry.

The individual is the product of his inheritance and of an ever-changing environment, and in his Gifford Lectures in 1937 Sir Charles Sherrington (1940) said, "but although of their species it is not quite like any other that ever was. It is not only man but it is the man John Brown, or the woman Mary Smith, whose exact like never was yet." In a recent book Dr. René Dubos (1960), of the Rockefeller Institute in New York, has much of interest to say on the subject of health and illness, and I would like to quote one short passage in which he writes: "Whereas the experimenter determines by choice the phenomena that he studies and the epidemiologist formulates statistically those most significant under the conditions he observes, it is the responsibility of the physician to decipher the relative importance of the various factors involved in the response of each individual patient and to decide which aspects of the internal and external environment can be safely manipulated for the purpose of treatment."

The Ecological Study of the Patient

Dubos is pleading for the biological approach to the problem of the individual and for the ecological study of each patient in order to assess the many factors in his ill-health and to treat him effectively. The family doctor is the person most favourably placed to know the factors that may be significant in each patient, both those genetically determined and those due to environment not only at the time of the illness but also during the earlier years of development. Hargreaves (1958), in his Heath Clark Lectures for 1957, expressed his belief that it is not until a graduate of the present time has had experience of family practice that he is able to appreciate any instruction or education in what to look for in such ecological studies. It would seem improbable that an average undergraduate would obtain the right attitude and appreciate the possible importance of social and minor psychiatric factors by a few attendances at special departments for these subjects, to which the physicians and surgeons of the hospital refer those patients whom they regard as suffering from causes they do not understand, but which they could understand had they the time to look for them with a knowledge of what they were looking for.

The undergraduate and house officer learn more from the example of the general physicians and surgeons whom they serve and respect than from any instruction, and the physician or surgeon in charge of the patient is the person who should be responsible for the social and psychiatric study and for the final assessment. The almoner is there, or should be, to obtain directly or through the local authority much of the evidence required, although special departments of psychiatry and social medicine should certainly be available when the methods and experience of a specialist are really necessary. In the last few years the hospital almoner has been freed to perform these services, for which she is trained, and in many hospitals she is now encouraged to act in co-operation with the physicians and surgeons and to provide the evidence they have rarely the time or opportunity to seek, and also to assist in teaching. There are not nearly enough almoners to serve the hospitals of the country efficiently, and even teaching hospitals have been slow to recognize the essential nature of the information they can supply.

Two recent publications—a book by Lady Wootton (1959) and the report of the Working Party on Social Workers under the chairmanship of Miss Younghusband—discuss in great detail the value and scope of almoners, health visitors, and social workers, and the need for many more; and there have been numerous shorter accounts of how health visitors and social workers can and do assist family doctors with their patients. In much the same way almoners are able to supplement the medical investigation of patients and the training of students and house officers in hospitals. At the World Conference on Postgraduate Medical Education in Chicago in 1959 it was generally agreed that postgraduate education in social medicine and psychiatry would remain ineffective until undergraduates were trained to appreciate the numerous social and community factors of ill-health, and this, I believe, will be accomplished only when the physicians and surgeons themselves set a good example by developing a biological

and ecological approach to every patient under their care. The factors disclosed may be of significance in aetiology; they are always significant for convalescence, rehabilitation, and the prevention of recurrences.

In a number of medical schools steps have been taken to introduce the undergraduate to the conditions met with in family practice, of which perhaps the most highly developed so far in this country is the General Practice Teaching Unit in Edinburgh under Dr. Richard Scott, and there are many experiments for the same purpose in the medical schools of the United States of America. Doubtless all these have value, but none can replace the example which the undergraduate should be given by all his teachers of how to discover and assess the social and emotional problems of each individual patient. Graduating with this tradition firmly established, every qualified medical practitioner, whether his career is in the hospital, general practice, or local authority services, will know how to make use of the wide range of assistance that local authorities now provide, and how they can help him in his patient-care and remove some of the causes, even if these be only contributory, of the ill-health and unhappiness of those who appeal to him for help and advice. Much has been said and written of the lack of co-operation between the three sections of the National Health Service, a lack due, I am convinced, to ignorance of what each has to offer and what each is competent to provide. There is little doubt that there has been a change during the past 50 years in the help that the individual member of the community seeks from the medical profession, a change that continues still and will require the constant adjustment of medical education and medical practice.

Integration of the Health Services

In his address to the British Medical Association in 1959, from which I have already quoted, Lord Adrian says: "It would be a great mistake to think that there can be a general advance without the support of every doctor who has patients to understand. We have ourselves to understand, too; however healthy and well balanced we may be there may be something to learn by observing our own reactions to difficult situations. At all events we have been trained to the clinical observation of human beings exposed to anxiety and discomfort and we must not belittle our training." Both general practitioners and consultants are able to contribute to this advance and to meet this challenge, and are more likely to do so earlier by co-operation not only with each other but also with the medical officers of the local authority and the social workers. Surely the senior physicians and surgeons of our general hospitals are the persons to take the lead in forming such a partnership, each for its own community.

Regular meetings of representatives of the three divisions of the National Health Service, and perhaps of the clergy also, in the area would soon show how each can best help the others and how the hospital and local authority services can utilize the peculiar experiences of family doctors to supplement their own restricted and specialized training. It seems probable that it was the observation of valves in veins that gave Harvey the clue to the circulation of the blood, and it may well be that some unforeseen observation will provide clues to be followed up by clinicians, physiologists, geneticists, psychiatrists, and social scientists that they may "search and study out the secrets of nature."

In the meantime the ecological study of each patient whom we are called upon to understand and to help must surely contribute to the health and happiness of the communities we have the privilege to serve.

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INITIAL EXPERIENCES WITH EXTRACORPOREAL CIRCULATION IN INTRACARDIAC SURGERY

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The technique of heart–lung by-pass for repair of intracardiac defects was placed on a firm foundation by Kirklin *et al.* (1955) and by Lillehei *et al.* (1956), and good results from these and other groups have established the soundness of the method. The following report concerns the first 25 consecutive such operations to be performed with the aid of a Melrose N.E.P. heart–lung machine (Melrose, 1955) at this hospital. Prior to the first human operation in September, 1958, practice by the complete operating team in the experimental laboratory had resulted in the long-term survival of seven successive sheep after 30 minutes' total heart–lung by-pass during which right ventriculotomy was performed.

Material

This initial series consists of 15 patients with ventricular septal defect (on one of whom two operations were performed), three with partial atrioventricular canal, one with atrial septal defect, four with congenital aortic or subaortic stenosis, and one with rheumatic tricuspid stenosis. Pre-operative haemodynamic findings are summarized in the Table in which the cases are grouped according to the major defect present and in which those with ventricular septal defect

are listed in order of decreasing pulmonary-to-systemic-flow ratio.

All 15 patients with ventricular septal defect were limited by dyspnoea. Effort intolerance was relatively slight, and was apparent only on fairly strenuous exertion in five (Cases, 3 7, 13, 14, and 15), but eight were unable to keep up with their companions during ordinary play. The remaining two (Cases 4 and 6) had been in congestive heart failure. None was cyanosed at rest, and, although blueness after effort was reported by the parents of three patients (Cases 8, 11, and 12), this was not apparent on clinical examination, and under conditions of cardiac catheterization the systemic arterial oxygen saturation was not reduced below the normal range.

The clinical features in five patients (Cases 1 to 5) pointed to ventricular septal defect with considerable left-to-right shunt, while the remaining patients (Cases 6 to 15) presented essentially as cases of pulmonary hypertension associated with communication between pulmonary and systemic circulations, the exact nature of which was established only after further investigation. In four (Cases 2, 5, 10, and 15) there was a parasternal early diastolic murmur, attributed, in the context of other features, to pulmonary incompetence. Impressive pulmonary ejection murmurs, accompanied by thrills, were present in four patients (Cases 2, 3, 5, and 15), in whom investigation revealed systolic pressure gradients across the pulmonary valve, and also in one patient (Case 8) where no such gradient was found. Clinical evidence of right ventricular hypertrophy was a constant finding, and this was supported by the electrocardiogram, which also showed a so-called partial right bundle-branch block pattern in all but four cases (Cases 4, 10, 13, and 14). While in the majority both the electrocardiogram and the character of the apex beat pointed to some degree of associated left ventricular hypertrophy there was in four patients (Cases 6, 11, 12, and 13) neither clinical nor clear electrocardiographic evidence of this (see Fig.).

The listing of these patients with ventricular septal defect in the Table, in order of diminishing pulmonary to systemic flow ratios, serves to group those with large left-to-right shunts without increase in pulmonary vascular resistance (Cases 1 to 5) and those where pulmonary hypertension was in part due to increased flow and in part to elevation of resistance. This elevation of resistance was relatively slight in two patients (Cases 6 and 7), but of at least moderate severity in the remaining eight. The data are, however, inadequate to enable the cases to be placed in the precise order of increasing pulmonary vascular resistance within these groups. In Case 15, for instance, the systolic pressure gradient between the right ventricle and pulmonary artery indicates that there was less increase in resistance than might otherwise be inferred, in the presence of equalization of right and left ventricular pressures, from the flow ratio alone. All other patients with systolic pressure gradients across the right ventricular outflow tract or pulmonary valve fall into the high-flow low-resistance group, and it is of interest that even in Case 3, where the gradient reached 60 mm., this was completely and immediately abolished by closure of the defect.

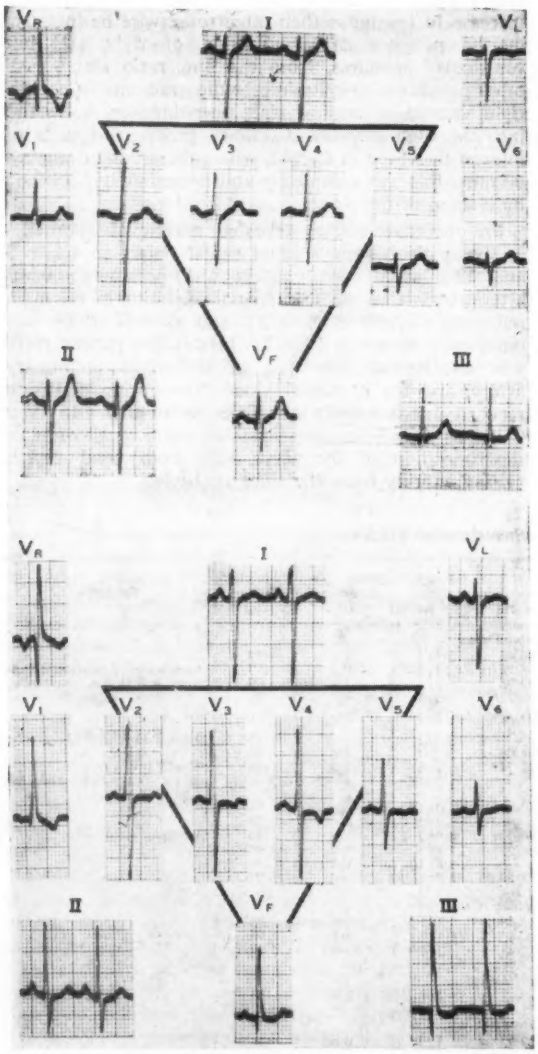
Pre-operative studies revealed additional anomalies in five patients—small atrial septal defect in Cases 3 and 12; atrial septal defect and persistent ductus arteriosus in Case 6; aneurysmal dilatation of the main pulmonary artery in Case 2; and absence of the left pulmonary artery in Case 7. In this last patient there was aneurysmal dilatation of the right pulmonary artery, and the bronchial blood flow during perfusion reached approximately one litre per minute. In Case 9 it was found at operation that there was complete dextroposition of the aorta, with both great vessels arising entirely from the right ventricle.

Pre-operative Cardiac Catheterization Findings

Case No.	Sex	Age	Wgt. (kg.)	Opn. No.	P.A. Wedge	Pressures† (mm. Hg)				Pulm. Syst. Flow Ratio	Pulm. Vasc. Resistance (R.U.)	Arterial O_2 Sat. (%)	Remarks
						P.A.	R.V.	L.V.	Aorta				
Ventricular Septal Defect													
1	M	6	20·5	16	4	36/16	42/–2	76/–3	76/42	3·5:1	—	95	
2	M	10	24·1	8	12	35/12	80/0	—	96/76	3:1	0·9	97	Aneurysmal dilatation L.P.A.
3	M	12	28·6	22	6	40/12	100/0	112/0	112/96	3:1	1·1	99	Small A.S.D.
4	F	6	29·1	6	15	62/26	62/2	—	98/72*	3:1	1·7	98	
5	F	10	26·4 22·7	1 7	14	76/36	96/2	—	102/68*	3:1	2·9	100	
6	F	2	12·3	25	6	92/50	92/4	92/4	—	2·5:1	—	98	Small P.D.A. A.S.D.
7	M	12	26·4	17	7	97/46	97/0	—	104/86	2·2:1	4·1	98	
8	M	7	14·1	10	2	76/44	78/2	—	112/74*	2:1	8·0	96	Absent L.P.A.
9	F	2	10·9	4	—	60/34	60/0	—	—	2:1‡	—	—	Origin both P.A. and Ao. from R.V.
10	M	5	14·1	5	6	78/50	78/2	—	—	2:1‡	—	—	
11	F	6	18·6	15	5	88/60	88/2	88/4	—	2:1	—	99	
12	F	6	21·4	24	4	84/44	84/0	84/0	84/60*	1·9:1	—	94	A.S.D.
13	F	5	18·2	19	8	92/46	92/0	—	90/55*	1·9:1	9·0	95	
14	M	6	22·7	3	19	100/48	100/4	—	—	1·8:1‡	8·4	—	
15	F	4	15·5	2	5	54/37	72/0	77/–2	77/50	1·8:1	—	97	
Partial Atrio-ventricular Canal													
16	M	8	23·6	12	6	27/6	33/4	104/6	—	2:1	0·9	95	
17	F	10	26·4	14	4	55/30	55/4	80/4	—	1·5:1	4·2	92	
18	F	8	30·9	23	1	25/15	25/1	96/1	—	2:1	—	97	
Atrial Septal Defect													
19	F	8	18·6	18	10	37/12	37/10	80/10	—	2:1	2·5	95	
Aortic Stenosis													
20	M	15	55·9	9	5	27/8	33/2	224/8	120/82	1:1	0·6	—	
21	M	24	64·1	11	—	—	—	120/4‖	74/44‖	1:1	—	—	
22	M	16	50·5	13	—	104/60	104/4	230/16	70/56	1·5:1	9·2§	90	Small V.S.D.
23	F	45	47·7	21	—	—	—	160/10	94/64	1:1	—	—	
Tricuspid Stenosis													
24	F	38	58·6	20	—	—	—	—	—	—	—	—	Moderate M.S.

* Brachial or femoral artery. †Zero level at sternal angle. ‡ Assuming 96% arterial saturation. § Total pulmonary resistance. ‖ Recorded at operation.

In all three patients with *atrio-ventricular canal defects* (Cases 16, 17, and 18) the lesion was of the partial variety with a cleft in the septal leaflet of the mitral valve and an intact ventricular septum. Symptoms were relatively slight in Case 18, but Case 17 was considerably limited by effort dyspnoea and fatigue, and Case 16 was in some degree of congestive heart failure at the time of operation despite intensive medical measures. In this last patient, heart failure with evidence of atrio-ventricular valve incompetence had developed three months previously after an attempt to repair the defect, using the atrial-well technique (Kirklin *et al.*, 1956). The patient had been submitted to operation by this method in the belief that the defect was probably an ostium secundum although minor discrepancies were present.



Electrocardiograms of two patients with ventricular septal defect and severe pulmonary hypertension, both showing at least moderate right ventricular hypertrophy but only equivocal evidence of associated hypertrophy of the left ventricle. Top: Case 11. Closure of the defect did not result in an immediate fall in P.A. pressure. The patient died 36 hours later. Bottom: Case 13. P.A. pressure was immediately halved by closure of the defect. Subsequent progress has been satisfactory.

Case 19, proved to have an ostium secundum type of *atrial septal defect*, was selected for repair by open heart surgery rather than by the atrial-well technique, which would otherwise have been used (Williams and Barratt-Boyes, 1959), because persistent elevation of venous pressure in the context of a relatively small shunt and only slight increase in pulmonary vascular resistance and an atypical electrocardiogram suggested a more complicated anomaly. The explanation of these discrepancies and of the unexpectedly severe episode of congestive failure which followed closure of this simple defect remains uncertain, but, other intracardiac defects and pericarditis having been excluded, an associated cardiomyopathy remains the probability.

Of the three patients with uncomplicated congenital *subvalvular aortic stenosis*, two (Cases 20 and 21) had minor symptoms, and only one (Case 23) was limited by effort dyspnoea during ordinary activities. In all three, however, the electrocardiogram showed changes, including ST depression and T inversion in left ventricular surface leads and their equivalents, indicative of considerable left ventricular hypertrophy. The one patient (Case 22) who had a *valvular aortic stenosis* and also a relatively small ventricular septal defect had deteriorated rapidly and progressively during the nine months prior to admission for surgery, and at the time of operation still showed gross cardiomegaly and incipient congestive heart failure in spite of treatment in hospital on a full medical regime for several months.

The single patient (Case 24) with *rheumatic heart disease* had severe tricuspid stenosis. An associated tight mitral stenosis had been partially relieved by valvotomy seven years previously. When admitted for surgery this patient showed gross systemic venous congestion, which was only partially relieved by preliminary intensive medical treatment. Open heart surgery was decided upon because of the danger of producing tricuspid incompetence by blind valvotomy.

Method

The details of the extracorporeal circuit and of the technique of perfusion are to be published elsewhere (Barratt-Boyes and Yarrow, 1961). Premedication was with promethazine, pethidine and hyocine according to body weight. Anaesthesia was induced with cyclopropane and oxygen, and was continued with these agents while cannulae for recording inferior vena caval and aortic pressures were inserted via the left femoral vein and artery (the latter by a Seldinger needle). Anaesthesia was then maintained by 75% nitrous oxide and 25% oxygen supplemented by thiopentone. For relaxation D-tubocurarine was used. During perfusion the lungs were kept gently inflated with pure oxygen.

The operative technique was essentially that described by Harshbarger *et al.* (1958) except that a median sternal split was employed in all but one patient, and the right common femoral artery was used for arterial inflow. Heparin dosage to the patient, initially 2.5 mg./kg. body weight, was later increased to 3 mg./kg. and the machine was primed with fresh warmed blood containing 18 mg. of heparin per pint (32 mg./litre). Potassium citrate arrest (Melrose *et al.*, 1955) was employed in all cases of ventricular septal defect and aortic stenosis, but the heart was not arrested for repair of partial atrio-ventricular canal and atrial septal defect, or for tricuspid valvotomy. During all operations the

inferior vena caval and aortic pressures, the mid-oesophageal temperature (by thermistor), and electrocardiogram were monitored, but continuous display of the electroencephalogram and arterial oxygen saturation (by ear oximetry) was undertaken only in the earlier cases. Multiple blood samples were taken for estimation of arterial *p*H, venous and arterial oxygen saturation, blood and serum haemoglobin, and serum electrolytes, and for culture. As an aid to blood balance the patient was weighed before and after perfusion, and timely replacement of post-operative blood loss was facilitated by continuous suction of chest drainage into graduated cylinders. The pressure cannulae were left in position for the first 8 to 12 hours to assist in the early post-operative management. In the immediate post-operative period fluid requirement was calculated on a basis of 800 ml. of 4.2% dextrose in N/5 saline per square metre of body surface area per day.

Perfusion Data

The length of by-pass varied from 7 to 57 minutes. Perfusion had to be stopped in Case 24 after seven minutes because the venous cannulae, which were not rigid enough, became kinked within the right atrium when they were retracted to give exposure of the tricuspid valve. Although sufficient time was available for an adequate tricuspid valvotomy the proposed direct-vision approach to the mitral valve was abandoned; and instead, after coming off heart–lung by-pass, a blind finger-fracture mitral valvotomy was performed using the right-sided approach of Bailey and Morse (1957).

The average flow rate during perfusion ranged from 36 to 89 ml./kg./min., with a mean of 67 ml./kg./min. for the 25 perfusions. Expressed as litres per minute, the pump output varied between 0.5 and 4.2. Although a high flow perfusion of 2.4 l./sq.m. of body surface per minute was aimed at it was not always attained. In addition to avoiding kinking of the venous lines, the most important factors in achieving a high venous return were the selection of venous cannulae which approximated as nearly as possible to the diameter of the superior and inferior cavae, and proper positioning of the metal tips of these cannulae just beyond the caval occlusion tapes. That technique improved with experience is suggested by the fact that the mean flow rate for the last 15 perfusions in this series was 72 ml./kg./min., an improvement of 12 ml./kg./min., on that obtained in the first 10. In all except Case 22, where the average arterial oxygen saturation was 82% at a flow rate of 4.2 l./min., oxygenation can be considered adequate, though it varied between 88 and and 100%.

Levels for serum haemoglobin in blood taken from the machine at the end of perfusion ranged from 10 to 65 mg./100 ml., while the average rise during the perfusion was 11 mg./100 ml. Readings of arterial blood *p*H were taken immediately before, during, and after perfusion and were continued at intervals of two to three hours for a further six to ten hours. These usually showed a mild alkalaemia prior to perfusion, the patients being moderately hyperventilated in the early stages of the operation and, with the exception of Case 22, either a mild acidaemia or alkalaemia in the immediate post-operative period. Blood in the machine was not warmed during perfusion, and the maximum temperature fall during operation ranged from 0.8 to 4.2° C. (average 2.3° C.).

Results

These operations were performed between September, 1958, and June, 1959, and while it is as yet too early to assess the final result the 21 surviving patients have shown progressive improvement with, in those who had congenital communications, reduction in heart size and often gain in body weight. There must be some misgivings, however, as to the future outlook of two patients (Cases 6 and 18) who have remained in complete heart-block, and of one patient (Case 5) who has significant aortic incompetence. The remote prognosis of patients with marked increase in pulmonary vascular resistance is also uncertain, though there is reason to anticipate that it will be favourable. The patients with subaortic stenosis should have an excellent prognosis, as excision of the obstructing diaphragm completely abolished the systolic pressure gradient in all three cases.

Details of the three deaths among the 24 patients are as follows:

Case 9.—In this 2-year-old infant both great vessels arose from the outflow tract of the right ventricle. The perfusion and surgical repair were both considered satisfactory. When the heart beat returned a 2:1 atrio-ventricular block was present which, apart from transient restoration of normal rhythm by isoprenaline on two occasions, persisted until four hours post-operatively, when complete block suddenly appeared and death followed a few minutes later. Necropsy confirmed that the semi-compressed "ivalon" sponge used for repair had completely corrected the defect. The ventricles were of equal thickness (7 mm.). Only 45 ml. of free fluid was found in the thorax. The lungs were free from significant oedema and from intra-alveolar haemorrhage. The medium-sized pulmonary arteries showed muscular thickening and intimal hyperplasia, these changes corresponding to early grade 2 changes of Heath and Edwards (1958). The brain and other systems showed no abnormality. Although the heart-block was probably sufficient cause for death this infant may also have been slightly hypovolaemic.

Case 11.—The ventricular septal defect in this child was 11 mm. in diameter and lay beneath the septal leaflet of the tricuspid valve (type 3 defect of Becu *et al.*, 1956). It was closed with a pledget of semi-compressed ivalon sponge. The perfusion was satisfactory in all respects, but two disturbing features were noted during operation. Firstly, there was greater hypertrophy of the wall of the right ventricle than in any other ventricular septal defect in the series; and, secondly, the pulmonary arterial and central aortic pressures remained identical after closure of the defect. The initial post-operative course was, however, quite uneventful. In the afternoon of the day after surgery the patient was a little restless and less alert, but there was no other evidence to suggest deterioration. That evening she suddenly vomited, had a convulsion, and lost consciousness. The heart was found to be in arrest, and cardiac massage was begun immediately but to no avail. At necropsy, accurate closure of the ventricular septal defect was confirmed. The right ventricle measured 11 mm. in thickness and the left 9 mm. There was no free blood in the chest. The lungs showed moderate acute oedema without intra-alveolar haemorrhage. The small and medium-sized pulmonary vessels showed marked pulmonary hypertensive changes with advanced fibrotic obliterative thickening, plexiform lesions, and some dilatation of arterial branches—early grade 4 changes of Heath and Edwards (1958). The brain and other systems were normal.

Comment.—Death at this juncture was unexpected and the precise mechanism of events leading to it remains uncertain. While proof that it was due to acute right heart failure is lacking, both the failure of pulmonary arterial pressure to fall after closure of the defect and the necropsy findings seriously question

whether pulmonary vascular resistance was not already too high to permit successful surgery; and this in spite of pre-operative data suggesting that pulmonary resistance was no higher than in some others in the series, and that pulmonary flow was approximately double the systemic flow. It is perhaps significant that in the two patients with similar pre-operative haemodynamic findings, in whom pulmonary artery and aortic pressures were measured after closure of the defect (Cases 12 and 13), the pulmonary artery pressure had fallen to approximately half the systemic level.

Case 22.—Because of the degree of cardiomegaly (C.T.R.=70%), the electrocardiographic evidence of gross left ventricular hypertrophy, and the persistence of mild congestive heart failure in spite of intensive medical treatment, this patient with congenital valvular aortic stenosis and small ventricular septal defect was clearly a poor surgical risk. At operation the ventricular septal defect was readily closed and the aortic valve gradient completely abolished. Ventricular fibrillation occurred, however, on attempting to restart the heart and proved most difficult to convert to normal rhythm. It recurred six hours post-operatively. A severe acidaemia (*p*H 7.16) also developed but responded to intravenous sodium lactate. Death occurred 20 hours post-operatively, the patient having failed to recover consciousness.

Comment.—Although this patient was a poor operative risk, death must be attributed to inadequate perfusion, for at a perfusion rate of 4.2 litres a minute (74 ml./kg./min.) the oxygen saturation of blood returning from the machine fell progressively during the 45 minutes of perfusion to a lower limit of 80%.

Post-operative Complications

There have been few serious post-operative complications in the survivors. However, as already noted, in Case 5 a second operation was required because of complete breakdown of the direct suture repair of ventricular septal defect on approximately the sixth post-operative day. After the second repair there is evidence of moderate aortic incompetence.

Post-operative bleeding has not been a problem after any of these 25 operations despite the fact that two patients (Cases 5 and 16) had had a thoracotomy within the preceding three months; and in only two patients did the total chest drainage exceed one litre. In three patients there have been minor complications from the left groin incision used for insertion of pressure cannulae into the femoral artery and vein. Post-operative sepsis elsewhere has not been encountered except possibly in Case 21, in which severe heart failure developed, associated with fever, elevation of sedimentation rate, and anaemia some 10 days after surgery, and which received intensive antibiotic treatment for presumed infective endocarditis, although confirmation from embolic phenomena or positive blood culture was not obtained. On the other hand, several patients, especially those whose heart failure was particularly severe, had low-grade pyrexia, lasting several weeks, which subsided spontaneously without any cause having been found.

Atrio-ventricular block of varying degree occurred in seven patients. In Case 9 the heart-block at least contributed to death; this has already been discussed. In four other patients (Cases 8, 10, 14, and 16) the block was of short duration and did not influence recovery in any way. In Cases 6 and 17, however, complete heart-block has persisted up to the time of writing, two and four months respectively after operation. In Case 17 direct stimulation of the myocardium by an artificial pace-maker via a wire electrode sewn into the right ventricular myocardium was required for approximately seven days. Both these patients have been given ephedrine and small doses of thyroid hormone (including initially l-triiodothyronine), but whether the subsequent gradual increase in pulse rate in both to between 55 and 65 is related to this treatment is uncertain.

Heart-failure with systemic venous congestion, usually readily controlled and of short duration, has been a prominent feature during the post-operative course. In Cases 16 and 24 failure was already present pre-operatively, and in Case 5 it was associated with breakdown of the initial repair of the defect, but all the remaining survivors, except Case 20, also showed some evidence of failure in the immediate post-operative period. The degree of failure varied from very slight to very severe, necessitating continuance of a full decongestive regime for two months or more post-operatively. It has tended to be greatest in those cases having a marked increase in pulmonary vascular resistance. The duration of hospital convalescence, which varied from 22 to 114 days, although influenced by other factors such as rhythm change (Cases 6 and 17) and post-operative infectious mononucleosis (Case 3), was fairly closely related to the severity of heart failure. All patients have, however, shown progressive improvement in the degree of failure, and although at the time of discharge the temporary continuance of digitalis has usually been advised, this has been merely a precautionary measure to prevent recurrence of congestion during further convalescence and resumption of more normal activity.

Discussion

While no conclusions of statistical value can be drawn from this report of our initial experiences with extracorporeal circulation in intracardiac surgery, some general comments would seem to be justified.

The importance of the preliminary trials in the animal experimental laboratory, when the team as a whole became familiar with the technique, is emphasized by the fact that these first 25 human perfusions were adequate in all but one case. In this patient the arterial oxygen saturation fell to unsatisfactory levels for between 10 and 15 minutes. It appears from our data that the Melrose oxygenator, as used in these perfusions, seldom gave 100% oxygen saturation of the blood, even when the flow rate was as low as 0.8 l./min., and that when the flow rate rose to more than 2.5 l./min., the oxygen saturation tended to fall. The results in this small series suggest, however, that an arterial oxygen saturation in the region of 90% is not detrimental to the patient, at least for perfusions of moderate duration. More recently, by enlarging the filming plates of the oxygenator, the total surface area for filming has been increased by approximately two-thirds. While the upper limit of performance of the oxygenator, modified in this way, has not as yet been firmly established it has proved capable of raising the blood oxygen saturation from a venous level of 73% to 90% or more at sustained flow rates of 4.25 l./min. Another modification yet to be undertaken is provision for temperature control of the blood in the machine.

In this initial series the problem of case selection has related almost entirely to patients with ventricular septal defect as the principal lesion, for, once the adequacy of the method was established, it was applied as the

technique of choice for relief of congenital aortic or subaortic stenosis and tricuspid stenosis, and for repair in cases where there was reason to suspect an atrioventricular canal rather than an ostium secundum type of atrial septal defect. Patients with ventricular septal defect as the principal lesion have been accepted for operation not because they appeared to be good-risk cases but rather because either a large left-to-right shunt or a marked increase in pulmonary vascular resistance argued for correction without delay. In the former group the anticipation that successful surgery would result in restoration of the circulation to normal is not in question, and it appears that even in those with considerable cardiomegaly and incipient failure the risks of operation are quite acceptable. On the other hand, it is widely recognized that the immediate operative risk increases greatly with progressive elevation of pulmonary vascular resistance, and that repair is almost certainly contraindicated when peripheral resistances in the two circulations are approximately equal with only slight residual left-to-right shunting. Moreover, it has yet to be shown that closure of the defect in patients with considerable elevation of pulmonary vascular resistance will necessarily lead to progressive restoration of the circulation to normal and improvement in the long-term prognosis.

To date the criteria which separate, even from the point of view of immediate risk, the operable from the inoperable among patients with moderate to considerable increase in pulmonary vascular resistance have not been finally established, and in this series the difficulty of selection is emphasized by experience with the one patient with anatomically uncomplicated ventricular septal defect who died. In this patient the clinical and pre-operative haemodynamic features did not differ significantly from those in others who responded favourably with an immediate fall in pulmonary arterial pressure to closure of the defect, yet repair of the defect in this case did not result in any fall in pulmonary arterial pressure, and at necropsy gross obstructive lesions were found in the pulmonary arterial tree. Our present policy is not to recommend closure of ventricular septal defects if the pulmonary to systemic flow ratio is less than 1.75:1 or the pulmonary vascular resistance is known to be greater than 10 resistance units; but this attitude may well require modification in the light of further knowledge and experience.

One of the cases of ventricular septal defect was complicated by both great vessels taking origin from the right ventricle, a fact not appreciated before operation. In this case there was no history or clinical suggestion of cyanosis and no polycythaemia, and at catheterization, already performed when surgery was not immediately in prospect, a sizable left-to-right shunt had been found. An arterial sample had not been obtained, and it is possible that measurement of arterial oxygen saturation, which would now be undertaken routinely, might have led to the diagnosis. On the other hand, patients with an apparently similar abnormality of the aortic origin but without reduction of arterial oxygen saturation below the normal range have since been studied, and it appears that selective angiocardiography may be necessary to exclude this complication with certainty.

Summary

An initial series of 25 consecutive heart–lung by-pass operations performed with a Melrose N.E.P. pump oxygenator is described.

In 15 cases ventricular septal defect was the principal lesion, and eight of these had at least a moderate increase in pulmonary vascular resistance. The principal lesion in the other nine cases was partial atrioventricular canal in three, atrial septal defect in one, congenital aortic stenosis in four, and rheumatic tricuspid stenosis in one.

Perfusion was regarded as adequate in all but one case in which the oxygen saturation of blood from the machine fell progressively, at a flow rate of 4.2 l./min. to 80%. By modification the oxygenating capacity has been improved.

There were three hospital deaths. The first of these occurred in a 2-year-old child, included in the ventricular septal defect group but in whom both the pulmonary artery and the aorta arose entirely from the right ventricle. The second death, attributed to the perfusion, occurred in an adolescent with severe congenital aortic stenosis associated with a small ventricular septal defect. The third occurred in a child with ventricular septal defect associated with a considerable increase in pulmonary vascular resistance.

Complete heart-block has persisted since surgery in one case of ventricular septal defect and one case of partial atrioventricular canal.

The technique of operation and problems of case selection are briefly discussed.

ADDENDUM.—Since submission of this paper a further 85 perfusions have been performed, bringing the total to 110. In the most recent 25 cases there have been four hospital deaths—namely, one case with corrected transposition with single ventricle; one with corrected transposition, pulmonary stenosis, and ventricular septal defect; one with tetralogy of Fallot; and one with congenital mitral valvular disease in which it was technically impossible to correct the mitral incompetence. Included amongst the 21 survivors are four cases of complete correction of tetralogy of Fallot.

We wish to express our thanks to the medical, nursing, and technical staff of Green Lane Hospital and to the Auckland Blood Transfusion Service for the contribution they have made to this work.

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"The mayor of the little commune of Aromas, near Dijon, has protested to his local prefect, claiming that his authority is being undermined by madmen. It appears that the 148 sane members of the village are outnumbered by the inmates of a local lunatic asylum, who in France are entitled to vote, and recently have been voting as a block for the opposition. The mayor's protests, however, seem to be based not on any inherent lack of judgment in the voters but on the fact that, coming from all parts of France, they should not be allowed to control the affairs of Aromas." (*The Times*, November 10.)

STAPHYLOCOCCAL BACTERAEMIA

CLINICAL AND BACTERIOLOGICAL OBSERVATIONS IN 201 CASES

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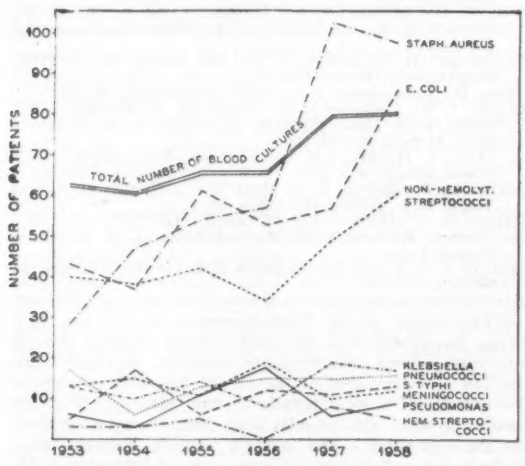
A recent survey of the cases of bacteraemia due to *Staphylococcus aureus* at a Danish hospital for communicable diseases showed a striking increase in the frequency of this disease during the last few years.

In order to find out whether this was a local phenomenon, a survey was made of all the cases of bacteraemia diagnosed at the Statens Seruminstitut and the Blegdamshospital. The accompanying Chart shows the number of patients suffering from bacteraemia due to some well-characterized organisms for each of the years 1953–8. The total number of blood cultures examined is given for comparison. It is evident that the most common bacteria isolated are *Staph. aureus*, *Escherichia coli*, and non-haemolytic streptococci.

In a corresponding investigation by Tarnowsky (1944), carried out in the years 1938–42, the dominating organisms were non-haemolytic streptococci, *Staph. aureus*, haemolytic streptococci, and pneumococci. The Chart shows that the two latter organisms have almost disappeared as a cause of bacteraemia, whereas the frequency of *Staph. aureus* and *E. coli* seems to have increased during the last few years.

The present report deals with the cases of staphylococcal bacteraemia in the above-mentioned material diagnosed in 1957 and 1958.



Cases of bacteraemia (1953–8) due to some frequently isolated bacteria. Cultivation performed at Statens Seruminstitut and Blegdamshospital, Copenhagen. The total yearly number of blood cultures is given in hundreds.

It is our purpose to account for the portal of entry, the source of infection, the phage-types, the antibiotic resistance, and some other properties of the isolated *Staph. aureus*, and to examine the influence of these factors on the mortality rate.

Material and Methods

The material comprises 201 cases of bacteraemia due to *Staph. aureus*, diagnosed at the Statens Seruminstitut and the Blegdamshospital. The 201 patients were admitted to 86 special hospital departments all over the country.

Clinical information, comprising diagnoses, signs of presumed or stated staphylococcal infections, possible source of infection, and portal of entry, was obtained through the use of detailed inquiry forms.

Phage-typing was performed at the Statens Seruminstitut, using the technique and the phages described by Wilson and Atkinson (1945) as modified by Williams and Rippon (1952) and Williams, Rippon, and Dowsett (1953).

Resistance to antibiotics was determined by the technique described by Jensen and Kjær (1947) and Dragsted and Erichsen (1953).

Production of alpha-toxin was determined by the method used by Jackson, Dowling, and Lepper (1955).

Production of hyaluronidase was ascertained by using a technique described by Faber and Rosendal (1960).

Egg-yolk reaction was performed as described by Gillespie and Alder (1952).

Results

Sex, Age, and Mortality.—The material comprised 124 males and 77 females. Six patients were under 1 year of age and 25 above 70. The distribution of patients within the in-between age-groups is rather uniform. Eighty-three (41%) patients died: 54 (44%) males and 29 (38%) females. The mortality rate for patients over 30 years was 51%, with only minor deviations for the subgroups, whereas only 19% of the patients under 30 died.

Complicating Diseases.—One-third of our patients had severe primary conditions which may have lowered their resistance. The diseases most frequently encountered were diabetes mellitus (21), generalized affections of the skin (15), and blood diseases (11). For the remaining 18 cases the diagnoses were: cancer (4), ulcerative colitis (3), shock (5), severe renal impairment (3), burns (2), and tetanus (1). Treatment with steroids had been given to 17 of these patients, and to a further three patients with minor disabilities. None of our patients received *x*-ray treatment. The mortality rate for this group of patients was 50%, as compared with 37% for patients with no complicating diseases.

Origin of Infection.—In 182 cases the information obtained permitted a distinction to be made between infections contracted outside hospitals and hospital-acquired infections. Table I gives the details. Probably a considerable number of the 19 cases in the group of infections of unknown origin were in fact nosocomial infections. The group includes four patients with cutaneous boils appearing shortly after admission to hospital, and several patients with infectious traumatic lesions, many of whom were treated by operations and intravenous infusions.

Patients Infected in Hospital

To give an impression of the character of the hospital-acquired infections, here are a few case reports.

Case 1.—A boy aged 1 month, who had been admitted to a dermatological department for pityriasis, developed bilateral pneumonia and bacteraemia with *Staph. aureus*, phage-type 80, resistant to penicillin and streptomycin. He died 36 hours after the first symptom of the infection.

Case 2.—A nurse aged 38 developed a boil on her nates. One month later she felt heavy pains over her back, which induced her to take large doses of analgesics. In order to break off this habit, she was admitted to a psychiatric department, where the diagnosis of bacteraemia was established (*Staph. aureus*, phage-type 80, resistant to penicillin and sulphonamides). *X*-ray examination revealed osteomyelitis in the lumbar spine. Complete cure followed antibiotic treatment.

Case 3.—A girl aged 6 years was infected with *Staph. aureus* (phage-type 80, resistant to penicillin, sulphonamides, and streptomycin) during an operation for complete dislocation of one of her hip-joints. Her symptoms were those of meningitis, endocarditis, pericarditis, bilateral pneumonia, and empyema; and several osteomyelitic foci with fistulae were found. Treatment for many months with antibiotics, gamma-globulin, steroids, and staphylococcal antitoxin resulted in eliminating the infection, but left the patient an invalid on account of the deformity in her pelvis.

Case 4.—A 61-year-old man had been treated with steroids for many years for rheumatoid arthritis. Two days after an intra-articular injection with hydrocortisone acetate had been given, he was admitted to hospital in a state of shock with bilateral pneumonia and a heavy pyarthrosis of his right knee. He was cured by intensive treatment with antibiotics and steroids, followed by surgery.

The portals of entry for infections acquired in hospital are given in Table I. The operations include gynaecological operations (7), prostatectomy (5), osteosynthesis (4), urethral catheterization (3), colectomy (2), and 14 miscellaneous operations each represented by one case only: herniotomy, appendicectomy, cholecystectomy, nephrectomy (renal tuberculosis), splenectomy (haemolytic jaundice); operations for stenosis of the mitral valve, paralysis of the urinary bladder, pilonidal fistula, stricture of the urethra, enchondromata, varices of the lower extremities, and malignant tumours of the urinary bladder, the pancreas, and the breast. Four cases originated from haemodialysis, six from intravenous infusions of injections, and in two cases the infection may have originated from traumatic lesions as well as from intravenous infusions and haemodialysis.

The group "miscellaneous and unknown" includes one patient with staphylococcal otitis media complicating pertussis, and one with cancer of the bowel; in the latter case bacteraemia followed oral antibiotic treatment. In 14 cases the portal of entry could not be ascertained with certainty, but in all these cases the infection started after hospitalization for a long period.

From the mortality rates in the present material it is concluded that infections due to surgical procedures have a higher mortality rate than those originating from cutaneous boils or pulmonary infections. The mortality rate for patients infected in hospital is higher than that for those infected outside hospital.

Patients Infected Outside Hospitals

The following are illustrative case-histories.

Case I.—A woman aged 31 acquired an infection from a scratch on her hand. One week later she was admitted to hospital, unconscious and pyretic. Within a few hours manifest shock developed. From the wound, nostrils, sputum, and blood *Staph. aureus* were isolated (phage-type 80, resistant to penicillin, sulphonamides, and streptomycin). Death followed after two days, in spite of prompt and intensive treatment with penicillin, erythromycin, gamma-globulin, staphylococcal antitoxin, and steroids, and general anti-shock therapy. No hospital contacts could be found.

Case II.—A 3-year-old girl contracted a boil on her leg and was admitted to hospital a few days later with bilateral pneumonia. She died after two days in respiratory failure, despite tracheotomy and use of a mechanical respirator. Necropsy revealed pyopneumothorax and multiple pulmonary abscesses. *Staph. aureus*, phage-type 80, resistant to penicillin and sulphonamides, was isolated from the blood and sputum. The infection could be traced to a sister of the patient, who had a boil on her leg, acquired during her stay at a home for children with infantile paralysis.

Case III.—A 19-year-old woman was admitted to hospital unconscious. She had been well until 12 hours before admission, when she had complained of headache. Investigations, including *x*-ray examination of the lungs and lumbar puncture, showed nothing abnormal. The next morning her condition deteriorated. She was then cyanotic and hypotensive; there was haemorrhage from the vagina and diarrhoea, and tiny pustules and petechia appeared; antibiotic therapy with penicillin, streptomycin, and erythromycin was started, and heavy doses of steroids were given for several days. She was pyretic, so treatment with chlorpromazine, pethidine, and transfusions was tried. She developed signs of oedema of the lungs, on account of which she was ventilated per respirator. In a few days she developed jaundice; blood-urea increased owing to anuria, and left-sided convulsions were observed. A transitory improvement was seen after haemodialysis, but the convulsions returned, and she died 11 days after the onset of the first symptoms. Necropsy revealed multiple cerebral abscesses and septic emboli in the heart and kidneys, ulcerative endocarditis of the mitral valves, pneumonia, and acute enteritis. *Staph. aureus*, phage-type 75/77, resistant to penicillin, sulphonamides, streptomycin, and tetracyclines, was cultured from blood, sputum, faeces, heart, kidneys, lung, and brain.

The portals of entry for the infections acquired outside hospital are given in Table I. One-third of these infections were secondary to cutaneous boils, but in 44 cases the portal could not be settled with certainty.

TABLE I.—*Origin of Infection and Portal of Entry in* 201 *Cases of Staphylococcal Bacteraemia*

Origin of Infection	Operations, i.v. Infusions, Haemodialysis, Injections		Cutaneous Boils, etc.		Respiratory Tract		Miscellaneous and Unknown		Total	
	No.	Died	No.	Died	No.	Died	No.	Died	No.	Died
Hospital	47	29 (62%)	31	13 (42%)	0	—	16	10 (63%)	94	52 (55%)
Community	4	2 (50%)	29	9 (31%)	11	4 (36%)	44	10 (23%)	88	25 (28%)
Unknown	0	—	4	1 (25%)	0	—	15	5 (33%)	19	6 (32%)
Total	51	31 (61%)	64	23 (36%)	11	4 (36%)	75	25 (33%)	201	83 (41%)

Most of the patients with primary osteomyelitis and endocarditis belonged to this group. Of the 88 patients, 25 (28%) died.

Phage-types

A total of 222 different strains were isolated from the blood of the 201 patients. The phage-types of these strains are given in Table II. It seems that nearly half of the nosocomial infections were due to phage-types 80 and 52/52A/80, and almost one-fourth to strains belonging to phage-group III. In 34 cases the infecting type was known to be endemic or epidemic in the hospitals concerned.

TABLE II.—*Phage-types of 222 Bacteraemia Strains*

	Origin of Infection			
	Hospital	Community	Unknown	Total
Phage group I:				
Types 80 and 52/52A/80	51	29	7	87
Other types	8	3	1	12
Phage-group II	10	17	2	29
,, III ..	26	19	8	53
N.I. and miscellaneous ..	3	8	0	11
N.T. (non-typable) ..	12	6	3	21
Not phage-typed ..	1	7	1	9
Total	111	89	22	222

N.I. = Not identified.

TABLE III.—*Mortality Rate for Bacteraemia Cases Due to Types 80 and 52/52A/80 Compared with that for Bacteraemia Caused by Other Types*

Origin of Infection	Phage-types							
	80		52/52A/80		Other Types		Total	
	No.	Died	No.	Died	No.	Died	No.	Died
Hospital ..	34	21 (62%)	15	7 (47%)	35	22 (63%)	84	50 (60%)
Community	19	8 (42%)	8	1 (13%)	53	14 (26%)	80	23 (29%)
Unknown	6	3 (50%)	1	(0)	10	2 (20%)	17	5 (29%)
Total ..	59	32 (54%)	24	8 (33%)	98	38 (39%)		

For infections acquired outside hospital the distribution of the various phage-types was more even.

An attempt was made to find out whether there was a higher mortality rate in bacteraemia due to type 80 and 52/52A/80 than in infections caused by other types (Table III). Patients infected with more than one strain have been omitted, as it is impossible to evaluate the individual roles of different strains in these cases.

Table III shows that the mortality rate for patients infected with type 80 + 52/52A/80 did not differ from that for patients infected with other types when groups of the same origin are compared (hospital, community).

Antibiotic Resistance

18% of the strains were sensitive to all antibiotics examined. Antibiotic resistance was most pronounced in hospital strains; nine-tenths of these strains were penicillin-resistant, and one-quarter tetracycline-resistant. Tetracycline-resistance was found in only 6% of strains acquired outside hospital. Fifty-eight out of 94 strains resistant to penicillin + sulphonamides + streptomycin, and 27 out of 38 strains resistant to tetracyclines were nosocomial strains.

Only 3 strains out of 213 were resistant to chloramphenicol, and no strain in this material was resistant to erythromycin.

Types 80 and 52/52A/80 were almost constantly resistant to penicillin, sulphonamides, and streptomycin, whereas chloramphenicol-resistance was found in only one and tetracycline-resistance in only two type 80 strains. Out of 38 strains resistant to tetracyclines 21 belonged to phage-group III. In the group of tetracycline-resistant strains three were sensitive to penicillin and streptomycin, and a further 14 were sensitive to streptomycin. Of these 17 strains with unusual antibiotic patterns, 16 were isolated from six patients with dermatological diseases admitted to departments where tetracycline ointments were often used.

The present material strongly confirmed the prognostic role of the sensitivity of the infecting strains to antibiotics. In Table IV resistance to three antibiotics is considered separately. The total figures show mortality rates for antibiotic-resistant infections one and a half to three times as high as for infections due to strains sensitive to the drugs in question. Resistance to several antibiotics made prognosis still worse: strains resistant to penicillin + streptomycin + sulphonamides were responsible for 90 cases, 53 of which were fatal. Of these 53 cases, 41 were nosocomial infections.

TABLE IV.—*Mortality Rate Related to Antibiotic-resistance of the Infecting Strains*

Origin of Infection	Penicillin		Streptomycin		Tetracyclines	
	Sens.	Res.	Sens.	Res.	Sens.	Res.
Hospital ..	6 (17%)	76 (63%)	22 (27%)	60 (71%)	66 (56%)	16 (75%)
Community	26 (19%)	57 (30%)	54 (24%)	29 (31%)	78 (26%)	5 (40%)
Unknown	3 (0%)	14 (43%)	7 (14%)	10 (50%)	15 (40%)	2 (0%)
Total ..	35 (17%)	147 (48%)	83 (24%)	99 (58%)	159 (40%)	23 (61%)

The figures in parentheses indicate mortality rates.

Out of 34 patients infected with organisms sensitive to the three above-mentioned drugs, only 5 died.

From Table IV it also appears that infections caused by resistant strains have a more favourable prognosis when they originate outside hospitals.

Alpha-toxin, Hyaluronidase, and Egg-yolk Factor

Taking mortality in bacteraemia cases as a measure of the virulence of the infecting organisms, we have used the present material to evaluate the pathogenic role of some *in vitro* properties of *Staph. aureus*. *Alpha-toxin* was produced in measurable amounts *in vitro* by 90% of the strains. The amount of toxin produced by the individual strains varied considerably (Jessen, Faber, Rosendal, and Eriksen, 1959), but showed no correlation to mortality.

The quantitative production of *hyaluronidase* likewise showed no relation to the clinical course of the cases.

However, a striking difference in mortality appeared when the cases were classified according to the *egg-yolk reaction* (E.Y.) of the infecting strains (Table V). The difference between the group of patients infected with egg-yolk-positive (E.Y.+) strains (mortality rate 36%) and those infected with egg-yolk-negative (E.Y.−) strains (mortality rate 67%) is highly significant.

TABLE V.—*Mortality Rate Correlated to Egg-yolk Reaction of the Infecting Strains*

Origin of Infection	Survivals		Deaths		Mortality Rate	
	E.Y.+	E.Y.−	E.Y.+	E.Y.+	E.Y.+	E.Y.−
Hospital ..	21	8	23	26	52%	76%
Community ..	47	5	16	5	25%	50%
Unknown ..	8	3	3	1		
Total ..	76	16	42	32	36%	67%

The material was closely scrutinized to discover whether this correlation was a primary one, or secondary to any known relevant factor. Only two such factors were shown to be of any importance: the epidemiological origin and the antibiotic resistance of the strains. Both these factors influenced mortality, and it was found that the E.Y.− strains occurred with the greatest frequency among hospital strains (Table V) and among antibiotic-resistant strains (Table VI).

TABLE VI.—*Mortality Rates for Infections due to E.Y.-positive and E.Y.-negative Strains Within Groups Uniform in Regard to Penicillin and Streptomycin Resistance*

	Survivals		Deaths		Mortality Rate	
	E.Y.+	E.Y.−	E.Y.+	E.Y.−	E.Y.+	E.Y.−
Streptomycin-sensitive ..	46	5	11	7	19%	58%
Streptomycin-resistant ..	29	11	28	25	49%	69%
Penicillin-sensitive	21	1	5	0	19%	
,, resistant	54	15	34	32	39%	68%

However, these two factors could not completely account for the higher mortality in bacteraemia due to E.Y.− strains. This higher mortality is observed even within groups of patients with infections of uniform epidemiological origin (hospital or community) (Table V). Furthermore, a comparison was made of the mortality rates for groups of patients infected with strains of uniform resistance to each of the antibiotics mentioned and various combinations of these antibiotics, but differing with regard to the egg-yolk reaction. This principle is illustrated in Table VI, where the comparisons are carried out within groups uniform regarding streptomycin- and penicillin-resistance. Corresponding comparisons were made with a view to the origin and the resistance of the strains. In comparable groups it was a constant finding that E.Y.− strains were responsible for higher mortality rates than were E.Y.+ strains.

Antibodies Against Alpha-toxin and Hyaluronidase

Increasing titres of antibodies against bacterial products can be expected 10 to 14 days after the beginning of an infection. In 118 patients surviving 10 days or more, antibodies against staphylococcus alpha-toxin (ASTA-T) and hyaluronidase (ASTA-H) were investigated at weekly intervals. In about 62% of the cases the antitoxin titres were elevated and the anti-hyaluronidase titres in 28%; in 72% of the cases the figures for at least one of the antibodies were elevated.

The antibody values were not correlated with mortality, with affection of certain organs, nor with the type of primary infection or the age of the patients. The values were independent of the *in vitro* production of alpha-toxin and hyaluronidase of the corresponding strains.

In infections due to strains of phage-types 80 and 52/52A/80 and to strains belonging to phage-group II, elevated ASTA-T titres seemed to occur more regularly (74%) than in infections caused by other types, whereas ASTA-H values were independent of the phage-type of the infecting strains.

Discussion

The increase (30%) in the number of specimens of blood received at the Statens Seruminstitut and the Blegdamshospital (Copenhagen) for examination during the period 1953–8 exceeded by far the 10% increase in the admission rate to Danish hospital departments. This preponderance is probably due to a greater interest in the bacteraemia problem during the last few years. However, the threefold to fourfold increase in the number of *Staph. aureus* bacteraemia cases would seem to indicate a real and considerable increase of this condition, and for the moment *Staph. aureus* is the organism most often isolated as the cause of bacteraemia.

In Australia, Hassall and Rountree (1959) observed a similar increase in 1955, and considered it to be due to the spreading of a particular staphylococcal strain, phage-type 80/81, which they had observed since 1953. The frequent occurrence of this type is now recognized in most parts of the world, and has been reported from England (Williams, 1959) and America (Blair and Carr, 1958), for example.

Phage-typing of staphylococcal strains isolated from boils, abscesses, paronychia, etc., going back to 1949 has shown that at that time type 80, sensitive to all antibiotics, was not infrequent in Denmark (Eriksen and Rosendal, 1960); but the first Danish nosocomial infections due to drug-resistant strains of type 80 were observed in 1954 (Thaysen, Eriksen, and Rosendal, 1957). In Denmark, as in England, type 80 during the last few years has replaced strains belonging to phage-group III as the most common cause of hospital staphylococcal epidemics. It is endemic in many hospitals and is widely distributed throughout the population (Dons, Eriksen, and Rosendal, 1960).

This shift of the predominating strain coincides with the increasing frequency of serious staphylococcal infections, especially nosocomial infections. However, it has not yet been convincingly shown that these two factors are causally related. If such a relation exists, it may depend upon a tendency of this type to cause long-lasting and easily spread infections, especially boils and paronychia, among hospital staff and patients. No difference in virulence—as measured by mortality in bacteraemia cases—could be ascribed to difference in phage-type in the present material.

The actual staphylococcal problem cannot be reduced to a question of the presence of type 80 strains. Only 83 out of 181 strains isolated from cases of bacteraemia belonged to this type or to type 52/52A/80. For nosocomial infections the figures were 49 out of 84 strains. This figure is surprising low, considering the wide distribution of these types.

Hospital-acquired infections probably account for a considerable part of the increase in the total number of staphylococcal bacteraemia cases in the present material, but a retrospective analysis of the epidemiological origin of bacteraemia cases during 5 or 10 years in order to confirm this view has not been possible.

In the two-year period investigated more than half of the infections in which the origin could be settled were nosocomial, and about 50% of these cases were directly caused by major or minor surgical procedures.

The hospital-acquired infections had a much poorer prognosis than infections originating outside hospitals. This bore no relation to the age of the patients, and the difference was found even when comparing patients with no serious complicating diseases to influence their

general resistance. The greater mortality rate when operation sites, etc., were the portals of entry (Table I) might explain some of the difference mentioned. The frequent antibiotic resistance of the hospital strains may also be of significance. It is unlikely, though, that ineffective antibiotic treatment of the cases caused by resistant strains explains the higher mortality rate in the "hospital" group. However, it was impossible to make a detailed evaluation of the treatment given, as the bacteraemia cases originated from 86 different hospital departments; but according to the antibiograms, which in most cases determined the treatment, chloramphenicol and erythromycin were effective in nearly all cases and tetracyclines in far the greater part. The possibility still remains, however, that endemic hospital strains achieve a higher virulence through human passages.

We used the material in an attempt to evaluate the possible influence of some bacterial properties on the mortality rate, being aware of the limited value of estimating the *in-vivo* properties through *in-vitro* experiments.

The production of alpha-toxin and hyaluronidase of the strains could not be shown to influence mortality, whereas a definite correlation could be established between mortality and the E.Y. reaction.

This reaction was introduced by Gillespie and Alder (1952) and Alder, Gillespie, and Thompson (1955). These authors suggested that the causative factor—probably a lipolytic enzyme—might be regarded as a pathogenic property. The reason for this suggestion was the predominance of EY+ strains in staphylococci isolated from boils and other closed purulent infections, and the frequency of E.Y.+ strains from human infections as opposed to animal infections. The first of these two observations has been confirmed by other authors (Tomlinson and Parker, 1956; Parker, 1958; Jessen *et al.*, 1959).

The present material shows a much higher mortality rate in bacteraemia cases due to E.Y.− strains than in cases caused by E.Y.+ strains. This observation is interesting in so far as no single biochemical property has previously been demonstrated to influence mortality in infections with *Staph. aureus*. The proportion of E.Y.− strains was highest in hospital-acquired bacteraemia cases and in strains resistant to antibiotics. This is in accordance with the above-mentioned reports by Gillespie and Alder (1952) and Alder *et al.* (1955).

The relation of the E.Y. reaction to the clinical character of the infection and to mortality in bacteraemia cases seems to encourage further research on biological differences between the two groups of strains. One of these differences seems to be the "serum opacity factor," stated by Tomlinson and Parker (1956) to occur almost exclusively in E.Y.− strains. There is no evidence that the absence of E.Y. reaction should be regarded as a defect due to the development of antibiotic resistance (Jessen *et al.*, 1959).

During recent years the question has arisen (R. E. O. Williams, 1959, personal communication) of whether there is any difference in virulence between type 80 and the closely related type 52/52A/80 (Asheshov and Rippon, 1959; Rountree, 1959). In the present material the proportion of E.Y.− strains and antibiotic-resistant strains was the same among strains of these two types; a comparison of virulence as estimated from an analysis of the mortality rate could not be carried out because of the small number of strains of type 52/52A/80.

The composition of the present material—epidemiologically unrelated cases of bacteraemia—renders it quite certain that the conclusions drawn regarding the frequency, the mode of infection, the mortality rate, the phage-types, and the biochemical properties of the strains are not influenced by particular local conditions in single hospitals or by the predominance of a few endemic or epidemic strains.

Summary

Out of 201 epidemiologically unrelated cases of staphylococcal bacteraemia, 94 were contracted in hospitals, and 88 outside hospitals; in 19 the origin of the infection was unknown.

In *hospital-acquired* infection the mortality rate was 55%. Of these cases 50% originated from surgical procedures and 33% from cutaneous boils. In half of the cases staphylococci belonging to phage-types 80 and 52/52A/80 were the infecting agents and in a quarter of the cases strains belonging to group III. Nine-tenths of the strains were penicillin-resistant and one-fifth tetracycline-resistant.

In infections contracted *outside hospitals* the mortality rate was 28%. In 44 cases the origin was unknown. In a third of the cases the infections originated from boils. One-third of the strains belonged to group I. 69% of the strains were penicillin-resistant. Only 6% of the strains were tetracycline-resistant.

The properties of the infecting strains were correlated to the mortality rate. No correlation was found concerning the production of alpha-toxin, hyaluronidase, or the phage-type.

Infections due to drug-resistant strains gave a higher mortality rate than those due to sensitive ones, and infections caused by egg-yolk-negative strains gave a higher mortality rate than those caused by egg-yolk-positive ones.

The levels of antibodies in serum against alpha-toxin and hyaluronidase showed no correlation to clinical features, mortality rate, or the *in vitro* production of these two substances.

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CYCLOPHOSPHAMIDE IN HODGKIN'S DISEASE AND RELATED DISORDERS

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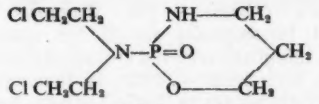
The value of the nitrogen mustards in the treatment of Hodgkin's disease and related disorders has been firmly established for many years (Gilman and Philips, 1946; Wilkinson and Fletcher, 1947). The limiting factor in their use has been their toxic action upon the bone-marrow and other tissues. These undesirable side-effects can be modified by the substitution of various radicals on the nitrogen atom. In this paper we report our experiences in the treatment of Hodgkin's disease and other tumours of lymphoreticular tissue with a cyclic nitrogen mustard phosphamide ester, cyclophosphamide (" cytoxan," " endoxan ").

Pharmacology

The pharmacological properties of the nitrogen mustards depend upon their β-chloroethyl groups (Goodman and Gilman, 1955). They are unstable in aqueous solutions: for instance, in the case of the methyl-*bis*(β-chloroethyl) analogue, intramolecular cyclization with the formation of biologically active quaternary immonium compounds occurs within a few minutes (Fig. 1). The biological activity of these drugs springs from their ability to attack nucleoproteins by combining with such of their component radicals as carboxyl, phosphoryl, or amino groups (Ross, 1953); it bears a direct relation to the rate of chloride dissociation (Fig. 1), which can be reduced by lowering the basicity of the nitrogen atom.

Cyclophosphamide, the derivative we have studied, was synthesized in 1958 (Arnold *et al.*, 1958a, 1958b) with the aim of preparing an inactive " transport " form of nitrogen mustard which would be activated only on reaching the site where its therapeutic effect was required. Malignant cells are known to be rich in phosphatases and phosphamidases; it was postulated that a nitrogen mustard phosphamide might well be split by these enzymes to an active form within the tumour. In addition, the P=O linkage of the phosphamide molecule lowers the basicity of the nitrogen atom and thus reduces the ionizability of the chloride (Arnold *et al.*, 1958b).

Cyclophosphamide is a cyclic nitrogen mustard phosphamide ester N_1N-*bis*(β-chloroethyl)-N^1-O-propylene phosphoric acid ester diamide with the following structure:



Unlike HN2 (mustine), it is stable in aqueous solution at 4° and 37° C. and is inactive *in vitro*, as shown by the viability of cell cultures in media containing it (Brock and Wilmanns, 1958). Further, the rate of chlorine-ion liberation is appreciably lower than that of other nitrogen-mustard derivatives. Its therapeutic index is high and no toxic action was observed on the liver or kidney, although a leucotoxic effect was evident. It proved effective in the rat against Yoshida ascites sarcoma, Walker 256 carcinoma, Jensen sarcoma, and DS carcinoma (Arnold *et al.*, 1958a; Brock, 1958; Burkert, 1958). In mice, cyclophosphamide was shown to be more active than HN2 against advanced L 1210 leukaemia as well as being effective against L 1210/AG-R leukaemia resistant to 6-mercaptopurine (Lane, 1959; Lane and Kelly, 1959).

Method

Of the 45 patients treated with cyclophosphamide, 17 had Hodgkin's disease, 3 lymphosarcoma, 1 reticulum-cell sarcoma, 1 lymphoid follicular reticulosis, 14 myelomatosis, 5 chronic lymphocytic leukaemia, 1 polycythaemia rubra vera, and 3 other tumours.

No particular criteria were employed for its use. Most patients received an initial intravenous course, beginning with 100 mg. and continuing at 200 mg. daily up to a total of 2 to 4 g. The drug was prepared by dissolving 200 mg. in 10 ml. of sterile water shortly before injection. The intravenous course was usually followed by the oral administration of 100 to 150 mg. daily in 50-mg. (1 tablet) doses. No *a priori* limits were set to the total amount administered to any one patient, many patients receiving long-term maintenance treatment, which varied from 100 to 150 mg. a day. The drug was temporarily withdrawn when satisfactory response was achieved or when toxic side-effects occurred. Frequent blood examinations were made on in-patients. In out-patient practice, a complete blood count every two or three weeks gave adequate control provided initial leucocyte levels were satisfactory.

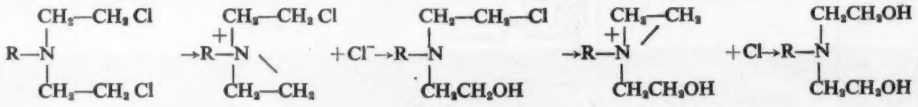


FIG. 1

The effects of treatment were judged by the patient's subjective impressions, such as diminution of pain or malaise, and by objective criteria. By objective improvement is meant control of fever, a diminution in tumour mass or hepatosplenomegaly, a gain in weight, a significant alteration in the peripheral blood picture or marrow cytology, or a return of the blood chemistry to normal. Change in any one of these parameters would be classified as objective improvement. Leucopenia is defined as a total white count of less than 4,000 cells/c.mm., and thrombocytopenia as less than 150,000 platelets/c.mm. Some patients were leucopenic before treatment began. In these, leucopenia is recorded as being due to the cyclophosphamide if the existing white count was halved.

Results

Hodgkin's Disease. — The diagnosis had been established histologically in all the cases. The 17 patients in this group received cyclophosphamide varying in quantity from 2,100 to 22,050 mg. (average 9,500 mg.). The results are shown in Table 1, Cases 1–17. Fifteen patients (88%) experienced subjective improvement after medication. Signs of objective improvement were present in 11 (65%). Side-effects occurred in 8 instances (47%) but were mild and did not require withdrawal of the drug, except in Case 5, in which the peripheral white count fell to 600 cells/c.mm. for a time. This patient had widespread disease in the terminal phase and died less than a month after the end of treatment. It is perhaps significant that this was the only case which developed a leucopenia in this group. No patient became thrombocytopenic.

In Case 1 the patient was bedridden and required frequent heroin for alleviation of pain due to spinal deposits. After cyclophosphamide it became possible to wean him from opiates. He became ambulant and relatively symptom-free for a time, but relapsed four months later.

In Case 2 the patient gained 11 lb. (5.5 kg.) in weight. Recalcification of osteolytic lesions in the skull and ribs is shown in Figs. 2 and 3. Subcutaneous nodules on the head became impalpable. This patient's symptoms returned soon after discontinuation of maintenance therapy. They have been partially controlled by resumed administration of the drug. Case 9 presented twice with a large palpable abdominal mass; response to cyclophosphamide has been prompt on both occasions. One patient (Case 17) was emaciated, profoundly anaemic, and febrile, with splenic enlargement and a mass of nodes in the left axilla. Six months later she was able to enjoy a holiday in San Francisco, having gained 2 st. (12.7 kg.) in weight and being free from all symptoms.

Myelomatosis.—This group comprises 14 patients. The results are shown in Table I, Cases 18 to 31. The dose of cyclophosphamide varied from 1,250 to 15,700 mg. (average 7,600 mg.). Six patients (43%) were subjectively improved; two were difficult to assess. Five patients (36%) showed objective signs of improvement as evidenced, for example, by regression of hypercalcaemia (Cases 19 and 26) and reduction in the proportion of plasma cells in the marrow from 50% to 23% (Case 24). This patient was relatively free of symptoms and did not notice any subjective change. Platelet counts in Cases 27 and 28 were low before cyclophosphamide was given. Cases 21 and 22 showed a rise in the platelet count from thrombocytopenic to normal levels. 11 (79%) cases showed leucopenia: this is in contrast to the findings in the Hodgkins group. The fall in the peripheral white count was particularly severe and prolonged in Case 18, who received cyclophosphamide and irradiation therapy at the same time. Thrombocytopenia was present in four patients (29%), but two of these had low counts originally.

TABLE I

Case No.	Sex and Age	Diagnosis	Duration of Disease	Previous Treatment	Dose of Cyclophosphamide (mg.)	Side Effects	Whether Improved	
							Subjectively	Objectively
1	M 28	Hodgkin's disease	4 yr.	Trimustine. DXR. HN2	6,000	—	+	+
2	M 43	,, ,,	1 ,,	Chlorambucil. DXR.	17,000	Mild alopecia. Transient vomiting	+	+
3	M 30	,, ,,	2 ,, 6 m.	DXR. HN2	2,100	Nausea	+	+
4	F 28	,, ,,	2 ,, 6 ,,	—	12,600	—	+	−
5	M 22	,, ,,	3 ,,	Prednisolone. DXR. HN2	3,150	Transient leucopenia	+	+
6	M 30	,, ,,	7 ,,	,, ,,	14,950	Transient nausea	+	+
7	F 30	,, ,,	2 ,, 2 ,,	DXR.	5,100	Leucopenia	+	−
8	F 39	,, ,,	6 ,,	Mannomustine. DXR. Prednisolone	22,050	—	+	+
9	M 27	,, ,,	4 ,, 9 ,,	DXR.	8,400	Transient nausea	+	+
10	M 22	,, ,,	4 ,,	,,	4,500	—	±	+
11	M 48	,, ,,	5 ,,	Cobalt therapy. DXR. HN2	4,500	Mild alopecia. Reduction in beard growth	+	+
12	M 17	,, ,,	2 ,,	DXR	10,000	—	+	+
13	M 43	,, ,,	2 ,, 6 ,,	Busulphan	9,450	—	+	−
14	F 18	,, ,,	1 ,,	—	5,250	—	+	−
15	F 27	,, ,,	5 ,,	—	6,250	—	−	−
16	F 27	,, ,,	2 ,,	—	14,700	—	+	−
17	F 23	,, ,,	4 ,,	DXR. Chlorambucil	15,600	Mild alopecia	+	+
18	F 52	Myelomatosis	1 ,, 9 ,,	DXR. Phenamidine	6,400	Leucopenia	−	−
19	F 43	,,	3 ,, 6 ,,	Transfusions	6,500	Leucopenia. Thrombocytopenia	+	+
20	M 51	,,	5 ,, 6 ,,	DXR	11,100	—	+	−
21	M 61	,,	1 ,, 4 ,,	DXR. Prednisone. DD4450. Transfusions	4,200	Leucopenia	±	−
22	F 46	,,	1 ,,	—	6,950	,,	−	−
23	F 67	,,	4 ,,	—	8,600	,,	±	−
24	M 54	,,	3 ,,	—	9,950	,,	−	+
25	M 50	,,	1 ,,	—	3,000	,,	+	−
26	F 53	,,	1 ,,	—	11,000	Thrombocytopenia. Leucopenia. Mild alopecia	+	+
27	F 47	,,	3 ,,	—	2,400	Leucopenia. Thrombocytopenia	−	−
28	M 61	,,	4 ,,	—	1,250	,, — ,,	−	−
29	M 41	,,	1 ,,	DXR	15,700	—	+	+
30	M 38	,,	3 ,,	M&B 938. DXR	14,800	—	+	+
31	F 62	,,	2 ,,	DD4450	4,500	Leucopenia. Mild alopecia	−	−
32	M 53	Lymphosarcoma	3 ,,	CB1348. DXR	1,100	Thrombocytopenia	−	−
33	F 51	,,	2 ,,	DXR	8,250	Mild alopecia	+	+
34	F 64	,,	7 ,,	,,	5,400	—	+	+
35	F 52	Reticulum-cell sarcoma	1 ,,	—	2,900	—	+	−
36	M 70	Lymphoid follicular reticulosis	4 ,,	Chlorambucil. DXR	2,850	—	+	−
37	F 63	Chronic lymphocytic leukaemia	3 ,,	—	1,050	—	−	−
38	M 59	,, ,,	1 ,, 6 ,,	Mannomustine	6,300	—	+	+
39	M 56	,, ,,	3 ,,	—	4,900	—	+	+
40	M 63	,, ,,	4 ,,	Chlorambucil	3,700	Leucopenia	+	−
41	M 62	,, ,,	3 ,,	,,	20,450	Thrombocytopenia	±	+
42	F 48	Polycythaemia rubra vera	1 ,,	32 P	4,200	,,	+	+
43	M 59	Ca. bronchus	3 ,,	—	1,050	—	−	−
44	M 48	Ca. rectum	5 ,,	Surgery	3,000	—	−	−
45	M 45	Liposarcoma	3 ,,	DXR. CB1348	3,000	—	+	−

Lymphosarcoma. Reticulum-cell Sarcoma. Lymphoid Follicular Reticulosis.—Of three patients with lymphosarcoma, one failed to improve. The other two, however, improved subjectively and objectively (Cases 33 and 34), although one exhibited a mild alopecia. The patient suffering from reticulum-cell sarcoma felt better after cyclophosphamide, as did the one with lymphoid follicular reticulosis. Neither showed objective signs of improvement. Dosage in the above conditions varied from 1,100 to 8,250 mg. No leucotoxic effects were observed, but one patient (Case 32) became thrombocytopenic.

Chronic Lymphocytic Leukaemia.—Three of five patients responded as shown by diminution of lymphadenopathy, decrease in size of the liver and spleen, and a fall in the peripheral lymphocyte count. Evidence for marrow remission is not available at the moment. One patient (Case 40) died of bronchopneumonia and his leucopenia was probably a terminal event. One patient (Case 41) has bronchial carcinoma as well as lymphocytic leukaemia. This thrombocytopenia is mild and the white count has been well controlled over seven months by a maintenance dose of cyclophosphamide.

Polycythaemia Rubra Vera.—This patient (Case 42) received 4,200 mg. of cyclophosphamide, the P.C.V. falling from 62% to 53% and the haemoglobin from 17.6 to 51.7 g./100 ml. The neutrophilia was likewise controlled. The platelet count was reduced, but as it had been low beforehand the significance of this is doubtful.

Other Tumours.—Two cases of carcinomatosis, one of bronchial and one of rectal origin, were treated with no effect. One case of widespread liposarcoma received cyclophosphamide with temporary subjective remission. One patient with bronchial carcinoma as well as chronic lymphocytic leukaemia (Case 41) has not shown any clinical or radiological evidence of spread of his cancer over seven months since cyclophosphamide was started.

Discussion

Cyclophosphamide has proved satisfactory in clinical usage. The amount given daily has been similar to that used by the German workers (Gross and Lambers, 1958). In contrast, Coggins *et al.* (1959) employ a loading dose of 7.5 mg./kg. body weight for six days followed by oral or intravenous administration sufficient to keep the white-cell count at 1,000–2,000 cells/c.mm. Alternatively, successive single injections of 45 to 100 mg./kg. body weight were used.

Most patients in the present series were given maintenance treatment of 100 to 150 mg. of cyclophosphamide daily following upon the initial course of the drug, and several patients (for example, Cases 2, 8, 16, 33, and 41) have been taking it regularly for

FIG. 2.—Case 2. Recalcification of Hodgkin's deposits in the third rib after treatment with cyclophosphamide. Radiographs taken on January 1 and July 30, 1960.

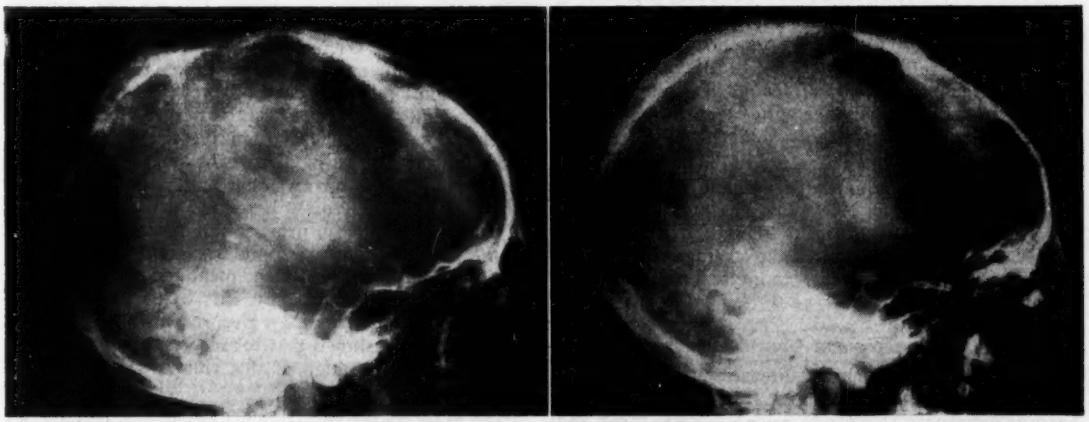


FIG. 3.—Case 2. Recalcification of Hodgkin's deposits in the skull after treatment with cyclophosphamide. Radiographs taken in February and July, 1960.

periods varying from four to seven months with beneficial effect. Some patients who experienced a return of symptoms when maintenance treatment was stopped obtained further relief by restarting cyclophosphamide. Somewhat similar conclusions were reached by Larionov (1956) using novoembichin.

Side-effects following upon the administration of cyclophosphamide have been inconspicuous in the present series. Alopecia has not proved troublesome, no venous thromboses occurred at the site of injections, and nausea and vomiting were infrequent, One male patient noticed a reduction in beard growth. In general, side-effects such as alopecia, sterile cystitis, gastro-intestinal disturbances, and transient fall in the haematocrit are met with more often when amounts in excess of 200 mg. of cyclophosphamide are given daily. Thrombocytopenia is said not to occur even at the higher levels of dosage (Haar *et al.*, 1960). In four of our patients, however, low platelet counts were found after treatment; two of these were suffering from myelomatosis.

The fact that of the 17 patients suffering from Hodgkin's disease 11 (65%) were objectively improved and that 15 (88%) benefited subjectively (Table II)

TABLE II

Diagnosis	No. of Cases	No. Improved	
		Objectively	Subjectively
Hodgkin's disease	17	11	15
Lymphoid follicular retic.	1	0	1
Lymphosarcoma	3	2	2
Reticulum-cell sarcoma	1	0	1
Myelomatosis	14	5	6
Chronic lymphocytic leukaemia	5	3	3
Polycythaemia rubra vera	1	1	1
Other tumours	3	0	1
Total	45	22 (49%)	30 (67%)

deserves note. Similar figures were obtained in other series (Gross and Lambers, 1958; Petrides and Moncke, 1958; Brichta *et al.*, 1958). Improvement may be expected 10 to 14 days after the beginning of treatment, the control of fever being a notable feature.

It is encouraging to find a 36% objective improvement rate in myelomatosis. Case 26 shows a particularly good remission, the serum calcium being reduced from 18.6 to 10.5 mg./100 ml. This patient gained 11 lb. (5.5 kg.) in weight; her haemoglobin rose from 6.2 to 9.2 g./100 ml. and has been maintained at the latter level. 11 (79%) cases of myelomatosis showed leucopenia during treatment, in constrast to the other groups treated.

Partial remission of chronic lymphocytic leukaemia was achieved in three out of five of our patients. However, Haar *et al.* (1960) could find evidence of marrow remission in only one out of their five cases that responded to treatment with cyclophosphamide.

Cyclophosphamide has been tried in a wide variety of other malignant tumours with variable effect (Lemke *et al.*, 1959; Baumann 1959; Coggins *et al.*, 1959). In one series (Coggins *et al.*, 1959), 18 out of 47 "evaluable" cases responded, the average duration of remission being two months. No improvement occurred in our three patients.

Summary and Conclusions

45 patients with malignant disease were treated with cyclophosphamide. 42 suffered from diseases of the haemopoietic or reticuloendothelial systems, three had disseminated malignant disease of other types.

Cyclophosphamide has proved a valuable addition to the chemotherapeutic drugs available for the treatment of malignant diseases of the haemopoietic and reticuloendothelial systems. It was found particularly effective in Hodgkin's disease, lymphosarcoma, chronic lymphocytic leukaemia, and myelomatosis, and it promises well in the treatment of polycythaemia rubra vera.

Side-effects are minor, although some depression of the white-cell count usually accompanies effective therapy. Maintenance treatment is safe, worth while, and simple, as the drug can be administered in tablet form. White-cell-count control is essential. Usually, while patients are on maintenance therapy, a count every three to four weeks will suffice.

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MEGALOBLASTIC MADNESS

BY

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The occurrence of mental symptoms in association with pernicious anaemia has been known for many years and been commented upon by various authors (McAlpine, 1929; Samson *et al.*, 1952; MacDonald Holmes, 1956; Wiener and Hope, 1959). Langdon (1905) drew attention to a group of cases in which nervous and mental symptoms preceded the onset of anaemia and described a great variety of neurotic and psychotic manifestations. Latterly (Wiener and Hope, 1959) the extreme variability of the symptoms has been stressed, and it is obvious that anything from a mild mood disorder to grossly psychotic behaviour may be encountered. Epilepsy, urinary and faecal incontinence in the absence of overt spinal lesions, dysphasia, and confusional states are also mentioned (MacDonald Holmes, 1956). Furthermore, it is well recognized that vitamin-B_{12} deficiency may give rise to optic atrophy, and it has been shown that tobacco amblyopia may be cured by administration of this vitamin (Heaton *et al.*, 1958).

The exact nature of the defect in cerebral metabolism which is produced by deficiency of vitamin B_{12} is not

understood. Studies of the cerebral blood flow and oxygen consumption by the nitrous oxide method (Scheinberg, 1951) show that the cerebral symptoms are due to the deficiency state and are not related to the degree of anaemia. Electroencephalographic studies of patients with pernicious anaemia (Walton *et al.*, 1954) show that abnormalities are common and that there is no correlation of the abnormalities either with the haemoglobin level or with age. Also, an abnormal E.E.G. was frequently obtained in anaemic patients who showed no evidence of subacute combined degeneration of the cord. The tracings in this series tended to improve 7 to 10 days after the beginning of treatment.

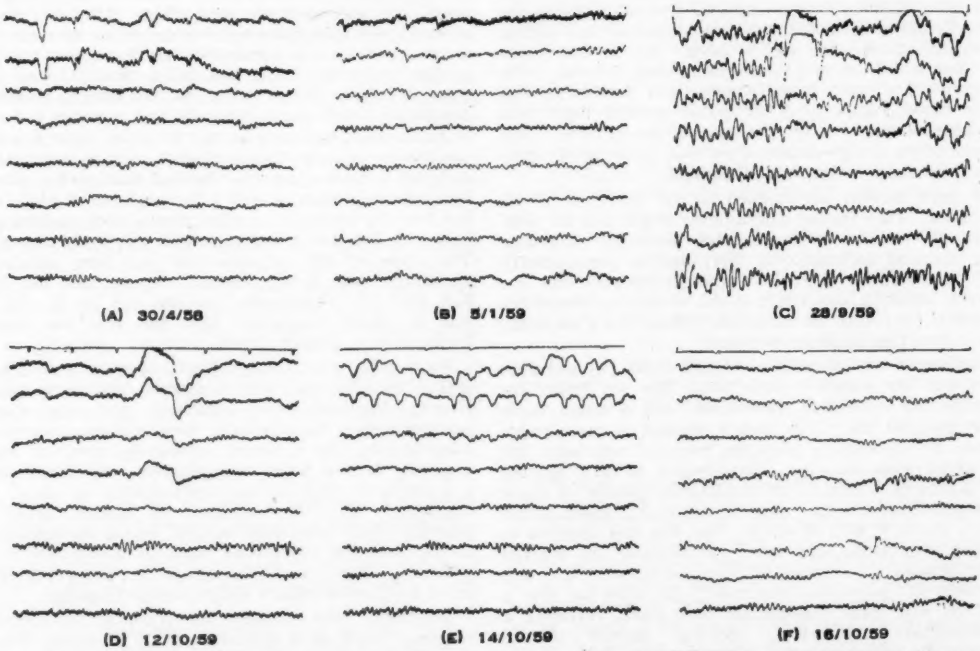
The occurrence of subacute combined degeneration of the cord prior to the onset of anaemia is well recognized and clinicians are now fully alive to this possibility. The time-lag may be considerable and may give rise to diagnostic difficulty unless this situation is constantly borne in mind. Owing to the many tragedies that have resulted from unawareness, with subsequent irreversible cord damage, it is now unusual to come across cases of this nature. It is quite obvious, however, that the importance of avitaminosis B_{12} in the production of cerebral symptoms, either localized or generalized, still needs to be increasingly thought of. The necessity for making the correct diagnosis cannot be overstressed, as delay is extremely dangerous and the condition eminently treatable, provided cerebral demyelination has not occurred. The histopathology of the cerebral lesions has been well established (Adams and Kubik, 1944), and it has been shown that they are essentially the same as those found in the spinal cord in subacute combined degeneration.

The following cases are presented as a reminder of the diagnostic difficulties that may be encountered when dealing with the cerebral manifestations of vitamin-B_{12} deficiency. It is also hoped to provide pointers on how the diagnosis may be made prior to the onset of anaemia, cord damage, or peripheral neuritis. It will be shown quite conclusively that absence of the diagnosis results not only in a steady deterioration of the patient's condition but also in considerable iatrogenic trauma, both mental and physical.

Case 1

A woman aged 48 was referred to the out-patient department in April, 1958, with a history extending over the previous nine years. Initially her symptoms had followed the death of her first baby at 6 weeks of age after 18 years of marriage. They consisted of sleeplessness, giddiness, and a feeling as if she was walking on air. In association with these generalized complaints she also described attacks in which she developed pain over the right eye, numbness of the face and right arm, and an inability to see properly because of a glaze across the right eye. Her tongue felt swollen, and she was unable to hold things in the right arm because of the numbness and pins-and-needles. During these focal phenomena she felt confused and unable to think clearly. These localized attacks would last for two to three days and then pass off.

At the beginning of this history the episodes were very infrequent indeed and she had remained fairly well until a few months prior to being seen as an out-patient. Her sister had recently died of bronchial asthma and the patient had nursed her through the terminal stages. After the sister's death the attacks became more frequent and were accompanied by severe depression. She was full of remorse, and insisted that her sister had died because she had not looked after her properly. Full physical examination at this time failed to reveal any abnormality. The haemoglobin was 92%, and an *x*-ray film of the chest normal. The diagnosis was thought to be depression with associated atypical migraine. However, an E.E.G. showed a definite generalized abnormality, maximal in the left hemisphere, with variable focal distribution. It was felt the possibility of multiple lesions (? vascular, ? neoplastic) should be



Case 1.—Serial E.E.G.s taken before and after treatment. Note the progressive generalized abnormality culminating in (C). Treatment was started on 10/10/59, and within 48 hours a striking improvement occurred (D).

considered. In spite of the abnormal E.E.G. the bulk of her symptoms were attributed to a guilt reaction connected with the death of her sister, and she was referred to the psychiatric department. The psychiatrist felt that time was the only thing likely to lessen her feeling of guilt, but asked the general practitioner to refer her again if her condition deteriorated.

She was not seen again until January, 1959, when referred to the psychiatric out-patient department. At this time she was in a confused state, unable to give a coherent account of herself and disorientated in time and space. The clinical picture was thought to be due to an organic confusional state, and the patient was accordingly admitted to a neurological bed.

On admission to the ward she said that during the previous week she had been suffering from severe headache affecting both frontal regions. These headaches were severe and had kept her awake. They were accompanied by transient attacks of dysphasia. She had felt suicidally depressed. The family history revealed that her father had died in his forties of paralysis of unknown nature and that one brother, in his thirties, had become paralysed, again without a known cause. Furthermore, a sister had died about 25 years earlier from "anaemia" while still in her twenties. Unfortunately the significance of these facts was not appreciated.

Examination at this time failed to reveal any definite physical signs in the central nervous system, apart from one observer commenting that joint position sense appeared to be defective in both upper and lower limbs. This was felt to be incapable of precise interpretation because of her confused state, and therefore ignored.

X-ray examination of the chest and skull, N.A.D. Haemoglobin 83%, with a normochromic film showing some anisocytosis only. Lumbar puncture, normal in all respects. Serum cholesterol, 200 mg./100 ml.; total serum lipids, 565 mg./100 ml. An E.E.G. showed a well-marked increase in abnormality compared with the previous record. The alpha rhythm was of lower voltage and more disorganized, while random intermediate slower components were more prominent in all areas and at times sharp waves were also present. The abnormal components now had a paroxysmal character. Maximum abnormality was clearly seen in the left sylvian region. It was reported that in view of the essentially diffuse disturbance and the deterioration a diffuse pathological disturbance was at work. An air encephalogram and a left carotid arteriogram were normal. The possibility of chronic hypoglycaemia was considered, but fasting blood sugars were all within normal limits and a glucose-tolerance curve showed no abnormality. She was placed on a high-carbohydrate diet, given small doses of anticonvulsant drugs, and discharged.

For three months she claimed to feel much better on this regime. Then further deterioration began and she complained of attacks of paroxysmal nocturnal dyspnoea. These sounded asthmatic in type, and a precautionary E.C.G. was entirely normal. Although mentally she was generally better, it was felt that she should be readmitted to hospital for further investigation. There was a six-weeks delay before this could be arranged.

Examination now revealed no change in the physical signs except that she looked a little pale. She was fasted for 24 hours and an E.E.G. performed, with a blood sugar of 70 mg./100 ml. The record showed a considerable increase in abnormality over the previous one, with left hemisphere preponderance. An injection of 50% glucose given during the tracing failed to change the pattern. A blood count performed on the same day showed a haemoglobin of 53% and a W.B.C. of 1,800. The film was reported as showing anisocytosis with some macrocytosis and marked polychromasia. Comment: "Film suggestive but not diagnostic of pernicious anaemia." In view of this a fractional test meal examination was made, revealing a histamine-fast achlorhydria. Sternal marrow showed characteristic megaloblastic haemopoiesis. The serum vitamin B_{12} level was 45 $\mu\mu$g. "Cytamen" 100 μg. daily was given and a maximum reticulocyte response of 22% was obtained six days after the initial injection.

Serial E.E.G.s were performed after the injection of vitamin B_{12}. On the second day it was reported that the E.E.G. was more stable than the one performed just before treatment (see Fig.). Two days later the E.E.G. showed a further slight but definite improvement (see Fig.). This improvement was maintained, although the left hemisphere showed a greater abnormality than the right. Isolated "sharp" elements were present in the left temporo-parietal region. Four weeks after the beginning of treatment the E.E.G. showed still further improvement, although some mild residual paroxysmal instability persisted in the left hemisphere.

The patient has been maintained on a dosage of 250 μg. of cytamen every 14 days. She remains very well from the mental and haematological point of view but continues to get nocturnal dyspnoea on occasion. Some 12 months after the commencement of therapy her E.E.G. remains improved although the mild abnormality in the left cerebral hemisphere persists.

Case 2

This patient, a woman aged 43, had been ill for 18 months with a depressive state. Six months after the onset of her symptoms she was seen by an experienced psychiatrist, who commented that although she was undoubtedly depressed he felt that there was a physical basis for her symptoms. He could find no underlying psychopathology to account for her depression and referred her to a general physician for a complete overhaul. Her main complaints were of headaches, sleeplessness, malaise, loss of appetite, and lack of interest in life in general. No organic basis was found for her symptoms, and admission was arranged to a mental hospital, where she was given a course of E.C.T. The E.E.G. at this time was normal.

It was stated that after this treatment she improved considerably. While under the care of the psychiatrists her haemoglobin was 82% and the film was reported as showing mild iron deficiency. She then returned home, but after three months broke down again and was readmitted to the mental hospital, where a further course of E.C.T. was given, again with an apparently good effect. After this improvement she was once more sent home, but her symptoms soon recurred, and it was noticeable that throughout this phase of fluctuation her weight had fallen steadily by at least a stone (6.4 kg.). Furthermore, she had become increasingly breathless, and on questioning admitted to having had attacks of paroxysmal dyspnoea for the preceding eight years. The past history revealed that four years prior to being taken ill with her present symptoms she had developed a moderate iron-deficiency anaemia with a haemoglobin of 55%. There had been no depression or other mental abnormalities associated with this, and it had responded effectively to oral iron. The cause of this anaemia had not been satisfactorily explained. The family history revealed that her mother had died of "thrombosis" at the age of 63 and there was a vague suggestion that she too was anaemic. Unfortunately further details were not available.

By now the patient was palpably anaemic, with a haemoglobin of 32% and film suggesting pernicious anaemia. Urgent admission was arranged, and the diagnosis confirmed by a megaloblastic bone-marrow, histamine-fast achlorhydria, and a serum vitamin-B_{12} level of only 25 $\mu\mu$g./ml. Jejunal biopsy was negative. An E.E.G. showed a medium- to high-voltage alpha-rhythm of about 9 c/s dominant. This was disturbed by random lower components, which were seen in mild degree throughout both hemispheres and which were increased moderately by overbreathing. The record was non-specific, but was considered to be compatible with a diffuse encephalopathy.

Treatment with vitamin B_{12} produced a reticulocyte response, reaching a maximum of 27% on the fifth day. On the second day the E.E.G. remained unchanged, but five days later there was a slight general improvement,

although the record still showed a mild and diffuse instability. Improvement was maintained, and after one month the record returned to normal.

Mentally she made great progress and her depression lifted. For the first time for 18 months she felt as if she had something to live for. Apart from minimal residual agitation she was well after the institution of vitamin-B_{12} therapy and continued to improve. However, this improvement was not maintained, and in spite of massive therapy she again began to deteriorate and remained in a perpetual state of mild agitation, although her haemoglobin was 92% and an E.E.G. completely normal.

Case 3

A 34-year-old woman was admitted to hospital as an emergency case in 1954. The general practitioner commented in his letter that she was complaining of severe depression, a sore tongue, and a sensation of electricity in the limbs. He queried whether vibration sense was lost below the knees. After admission it was discovered that she had been behaving peculiarly for some months. For a few weeks before admission this had culminated in marked ideas of reference and a refusal to leave the house. She was convinced that she smelt offensively, and consistently warned her children not to eat the food she had prepared. On the evening of admission she had made an attempt at suicide by drowning. She admitted to auditory hallucinations but was unable to give a coherent account of her voices. Her stepdaughter volunteered the information that a month previously she had "fainted" several times. The past history contained no illnesses of significance. The family history revealed that her father committed suicide by coal-gas.

On examination she was agitated and tearful, and in view of the profound mental disturbance it was felt wisest to transfer her to the mental observation ward. A note was made that she was not clinically anaemic and that the spleen was not palpable. Sensory testing of the C.N.S. proved impossible, but no qualitative changes in the reflexes were noted. She continued to show severe mental disturbance, and this resulted in her being certified and transferred to a mental hospital, where she was admitted in a semi-stuporous state and unable to give an adequate account of herself. A diagnosis of depression was made.

A course of E.C.T. was started and after about 12 applications she appeared to be improving, the personality emerging being of a cheerful and contented nature. After five months she was thought to be well enough to start going on leave. This was extended at the patient's request. But when seen again as an out-patient one month later she complained of dizziness, headaches, and not feeling well generally. Further investigation was refused.

Shortly after this she was readmitted to an acute medical bed and found to be severely anaemic with a haemoglobin of 28%. A diagnosis of pernicious anaemia was fully substantiated by the usual investigations and a maximum reticulocyte response of 32% obtained to intramuscular vitamin B_{12}. Her mental state greatly improved after the institution of treatment, and apart from some residual hypochondriacal anxiety she remained well five years later. Questioning revealed that she went grey at the age of 22 years.

Case 4

A woman aged 64 was admitted to hospital in May, 1954. Her previous history revealed that pernicious anaemia had been diagnosed 20 years earlier and a course of liver sandwiches commenced. She had failed to tolerate these and remained under the care of her general practitioner on iron therapy alone.

In 1949 she had been admitted to a mental hospital suffering from "atypical depression." Here the diagnosis of pernicious anaemia was substantiated, but it was considered that her mental symptoms justified a course of E.C.T., and this was given. Intramuscular "anahaemin" was begun. She remained in the mental hospital for six months and was then discharged as much improved. After discharge her mental state was considered to be quite normal, apart from periods of "excitement" which she related to the liver injections. These periods of mental disturbance were so profound that she had felt justified in refusing further injections about 12 months prior to the present admission.

Examination now revealed her to be anaemic (haemoglobin 42%) and mentally strange. No abnormalities were detected in the central nervous system. Although orientated in all spheres she was prone to talk nonsense. Intramuscular vitamin B_{12} was started and a maximum reticulocyte response of 27% obtained. She was placed on a maintenance dose of 250 μg. every two months and followed as an out-patient. Two months after discharge she felt very well and seemed mentally better. However, one month later she was again admitted to the observation ward as a case of mania, certified, and transferred to a mental hospital. At this time she was very disturbed indeed and displayed a well-marked flight of ideas. She apparently improved rapidly after a short spell in the mental hospital and discharged herself. When seen again as an out-patient one month later she ascribed her manic phase as being due to the cytamen injections, which she said were mescaline. Her haemoglobin was 88%.

She continued to attend as a out-patient, and in 1955 had a further nervous breakdown, for which she again entered the mental hospital and received E.C.T. Some improvement was said to follow this, and she was once more discharged but continued to attend as an out-patient. Mental fluctuation persisted. Two-and-a-half years after the beginning of cytamen therapy the dosage was increased to 400 μg. every two months. Since then she has remained perfectly well and her nervous symptoms have been completely eradicated.

Case 5

This case is only briefly mentioned. A man of 56 who had a previous history of partial gastrectomy for peptic ulceration was referred to the out-patient department because of headaches. The headaches formed a small portion of a bizarre symptomatology which was felt to be depressive in nature, but in view of his previous operation estimations of a full blood count and serum vitamin B_{12} were ordered. The blood count was normal in every respect, but the vitamin B_{12} was found to be only 105 $\mu\mu$g./ml. As this figure was below the accepted lower normal of the laboratory in which the investigation was made, the test was repeated on a separate occasion and the figure confirmed. Sternal marrow showed a normoblastic reaction.

Questioning of the patient revealed that since his gastrectomy he had been generally unwell apart from one occasion when his doctor had given him liver injections for six weeks on a purely empirical basis. Numerous placebos had failed to influence his symptoms.

Treatment with massive doses of cytamen (1.000 μg.) was started, and four days later the patient claimed to be symptom-free. At the time of writing it is far too early to say whether this improvement is going to be maintained.

Case 6

A woman aged 46 was admitted from a mental hospital with gross signs attributable to subacute combined degeneration of the cord. She had previously been leucotomized for depression without any improvement in her mental state being produced. Unfortunately, the rather bizarre symptomatology which her cord damage and peripheral neuritis had produced was considered to be part of the pattern of her mental illness, and a long delay ensued before the correct diagnosis was established. By the time of her admission to a general hospital she had a spastic paraplegia with enormous sacral bedsores and a megalo-

blastosis in the peripheral blood. In spite of massive supportive and remedial therapy deterioration steadily continued until her death.

Discussion

No excuses are offered for re-emphasizing the importance of diagnosing megaloblastic madness. Although the condition is mentioned by many authors, there has been little documentation of cases presenting with clinical manifestations in the absence of anaemia or subacute combined degeneration of the cord. The six cases described in this paper have been drawn from a much larger number in order to illustrate the various points thought worthy of mention.

In Case 1 the history extended back 10 years and the presenting features were a mixture of depression and peculiar focal attacks. There appeared to be adequate psychopathology to account for her depression, which was initially felt to be the predominant feature of the illness and led to referral to the psychiatric department. The only abnormal finding at this time was the generalized E.E.G. abnormality, and the importance of this was overlooked. A delay of nine months then ensued before it became obvious on clinical grounds that she was suffering from an organic condition. Further deterioration in the E.E.G. in the absence of focal neurological signs or anaemia led to many diagnoses being considered and appropriate investigations undertaken. The importance of the family history was overlooked and, although commented upon at the time, the association between anaemia, obscure paralyses, and the patient's clinical condition and grossly abnormal E.E.G. was not appreciated.

It is well known that sufferers from pernicious anaemia look and feel much better the day after the initial injection of vitamin B_{12}. This, of course, bears no relation to improvement in the haematological picture. In Case 1 a similar improvement was noted, and there was a striking reduction in the E.E.G. abnormality on the second day after the commencement of treatment. Although the E.E.G. continues to show serial improvement a suggestion of a left temporal focus still remains, and it seems probable that an area of cerebral demyelination has occurred. This focus is compatible with the focal attacks of which she complained, although these have now completely cleared up. It is possible that her persisting attacks of nocturnal dyspnoea have a temporal-lobe aetiology, and it is of interest that Case 2 also gave a history of this symptom without an obvious cause being found.

Case 2 emphasizes further pointers to the consideration of the correct diagnosis. "Nervous breakdowns" occurring with a previously good mental history and a negative family history of mental instability should encourage the observer to think very hard. Furthermore, there was no obvious psychopathology to account for her symptoms, and a very experienced psychiatrist was of the opinion that the patient was physically ill. In this particular case the initial E.E.G. was normal, and it is obvious that the diagnosis could only have been made by having a healthy clinical suspicion that avitaminosis B_{12} might be the cause.

The psychosis exhibited by Case 3 was obviously of such a nature as to overshadow any consideration of an underlying organic cause. Nevertheless, in retrospect, there were several signposts in the history that pointed the correct clinical path. These facts were ignored on admission, and owing to her disturbed mental state it was impossible to obtain the patient's co-operation in full neurological examination.

Case 4 illustrates a pattern of mental illness occurring within a known diagnosis of pernicious anaemia. Here the patient had failed to maintain her treatment because she developed a fixation about her injections. When finally "rediagnosed" she was placed on a maintenance dose of 250 μg. of vitamin B_{12} every two months. In spite of this she continued to display abnormal mental behaviour, although her haematological picture was normal. When the intake of vitamin B_{12} was doubled she became mentally well and has remained so. The importance of giving increased doses of vitamin B_{12} to sufferers from subacute combined degeneration of the cord is well recognized, and it seems logical, and necessary, that those with evidence of cerebral vitamin-B_{12} deficiency should be treated likewise. This fact, however, may not be fully appreciated.

In the absence of signs or symptoms of cord or nerve damage the importance of assessing the patient's mental state before dosage is evaluated is often overlooked. Mental changes may be attributed to the anaemia *per se* and inadequate therapy result in irreversible cerebral damage. It seems probable that Case 2 has been left with a degree of cortical damage that no amount of treatment will eradicate. The past history of this case revealed an iron-deficiency anaemia which had responded fully to oral iron. Recent work (Cox *et al.*, 1959) shows that low serum vitamin-B_{12} levels may be associated with iron-deficiency anaemia and a normoblastic bone-marrow, and, futhermore, that the vitamin-B_{12} level rises with the correction of the anaemia by iron alone. Normoblastosis with vitamin-B_{12} levels of under 120 $\mu\mu$g./ml. is a new concept, but it adds weight to the fact that the symptoms of which Case 5 complained were in some way related to a chronic insufficiency of the vitamin.

Our present concept of normal and abnormal serum vitamin-B_{12} levels has been built up by consideration of the presence or absence of pernicious anaemia and/or subacute combined degeneration of the cord. Most workers accept a lower limit of normal as lying between 100 and 150 $\mu\mu$g./ml. This is almost certainly untrue, as a mean level of 218 $\mu\mu$g./ml. was found in tobacco amblyopia (Heaton *et al.*, 1958), as opposed to a level of 538 $\mu\mu$g./ml. in normal controls. Unfortunately, bone-marrow studies were not performed in this series, but it seems probable that normoblastosis would have been found in most of the cases, although damage to the central nervous system was being produced. The high percentage of the population who smoke renders it possible that this fact may play a part in the production of other manifestations of vitamin-B_{12} deficiency. These may be subtle, and be confined to the cerebrum and easily dismissed as psychiatric disorders.

The efficacy of vitamin B_{12} as a tonic is a matter of scientific dispute. Nevertheless its use as a panacea of all ills has probably been founded on some sort of evidence, and it seems likely that its reputation in this connexion has been due to the fact that occasional sufferers from deficiency of the vitamin have received it as part of a blunderbuss or psychotherapeutic regime and dramatic improvements duly noted. Depression after gastrectomy for peptic ulceration is well recognized by psychiatrists, and it may well be that these patients are suffering from a chronic insufficiency of vitamin B_{12}. In this type of case there is a danger of accepting

the patient's mental symptoms as being due to the "ulcer type" or that he is being "difficult" after the operation.

Finally, it is emphasized that the diagnosis is difficult to establish in many cases in spite of a healthy clinical suspicion. Present-day "normal" levels of serum vitamin B_{12} are inadequate to cope with a wider concept of deficiency of the vitamin, but blind administration is to be deprecated unless injections are to be continued for life if the patient improves.

Summary

Attention is drawn to the pre-macrocytic (? pre-megaloblastic) state, and six cases are presented to illustrate the pitfalls in diagnosis.

Apart from the mental state, an abnormal E.E.G. may be the only positive finding and suggest exclusion of the diagnosis.

Much larger doses of vitamin B_{12} are needed when treating this type of case, and care must be taken to ensure that an associated encephalopathy is not missed in a patient who presents with severe anaemia. Attribution of the mental symptoms to the anaemia may result in undertreatment, with subsequent cerebral demyelination as the physician's reward.

It is probable that both exogenous and endogenous factors may modify the body's need and demand for vitamin B_{12}. The role of smoking as a possible factor in the production of syndromes other than tobacco amblyopia is worth future consideration. Our present concept of normal levels of the vitamin needs constant re-scrutinization and evaluation in order that treatment may be planned on a scientific basis.

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On August 31 this year, the number of children in the care of London County Council was 8,830 (5,083 boys and 3,747 girls). This figure was 200 more than on August 31 last year. The largest increase was in children under 5 years of age (2,100 compared with 1,999 on August 31, 1959). Of the children in care 939 were "short stay" children—that is, they were in care for such temporary causes as the illness or confinement of a parent—compared with 852 "short stay" children last year. Considerable success has been achieved in finding foster homes. This year it was possible to board out 2,061 children compared with 1,884 last year. (L.C.C. Council Meeting, November 22, 1960.)

MILD HEREDITARY SPHEROCYTOSIS —A FAMILY STUDY

BY

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The clinical features and laboratory findings of typical hereditary spherocytosis are well known and have been reviewed by Dacie (1954). The condition may also occur in a mild form, when clinical and laboratory findings are minimal (Gänsslen, Zipperlen, and Schüz, 1925; Campbell and Warner, 1926). Families suffering from mild hereditary spherocytosis have been described by Discombe (1948) and by Young, Izzo, and Platzer (1951). Affected members in these families showed similar manifestations of the disease.

There is fairly general agreement in the medical literature that the disease, whether in the severe or the mild form, is transmitted as a Mendelian dominant characteristic (Race, 1942). However, some families show irregularity in the pattern of inheritance. Thus Race found a significant shortage of affected sibs compared with the expected ratio. Young (1955) described five families in each of which both parents of an affected child seemed to be haematologically normal. In at least two of these families, mutation could be excluded as another member of the kindred also suffered from spherocytosis. Young concluded that carriers might occur in families with hereditary spherocytosis who could transmit the genetic defect but themselves appear normal. Ham (1955) confirmed Young's observations, and pointed out that minor increases in mean corpuscular haemoglobin concentration or osmotic fragility of incubated red cells might be important in detecting the carrier state.

The present paper describes three generations of a large family with mild hereditary spherocytosis. In this family two carriers were identified who appeared to be haematologically normal when first examined. Repeated testing of one of these carriers disclosed an abnormality on the fourth occasion. The difficulties in diagnosis offer one explanation for the shortage of affected sibs found by Race.

Family Study

The proband was a 26-year-old man (Fig. 1, Subject II 4) with no significant past history except "failure to thrive." He was admitted to hospital suffering from a fractured pelvis sustained in a motor-vehicle accident. The amount of blood loss was uncertain, as a large haematoma of the thigh was present. The haemoglobin value of his blood three days after admission was 7.6 g./100 ml. and he was given a transfusion of 1 litre of whole blood. At this time spherocytes were noted in the blood film. No operative procedures were performed. Four days later the haemoglobin value was 9.4 g./100 ml., haematocrit 27%, and reticulocytes 8.6%. The serum bilirubin was 1.5 mg./100 ml. and red-cell osmotic fragility was increased. The direct Coombs test on his red cells gave a negative reaction. Further clinical examination revealed slight icterus; the spleen was not palpable. Apart from short stature, the patient was normally developed.

No specific therapy was given for the anaemia after the initial blood transfusion, and the haemoglobin value returned to normal during the next few weeks. However, reticulocytosis, spherocytosis, and increased osmotic

fragility persisted. The Table shows a representative blood count performed six months later.

With the co-operation of the patient, a study was made of available relatives, most of whom consented to clinical and laboratory examination. No member of this family had been diagnosed as suffering from hereditary spherocytosis.

Methods of Family Study.—Clinical study included history, general inspection, and palpation of the abdomen. Venous blood was obtained for haemoglobin value, haematocrit, reticulocyte percentage, blood-film examination, and red-cell osmotic fragility according to the methods described by Dacie (1956). In two members the osmotic fragility of incubated red cells was determined.

Results

The findings in those members of the family who were examined are shown in the Table. The code numbers refer to the individuals listed in the family pedigree in Fig. 1. Four members of generation I were examined. One member (Subject I 5), the father's sister, was diagnosed as suffering from hereditary spherocytosis. She had splenomegaly, reticulocytosis, spherocytosis, and increased red-cell osmotic fragility. This patient also had a palpable liver and a past history of gall-bladder colic. She was not anaemic. Neither parent of the proband (Subjects I 2 and I 3) had clinical or laboratory evidence of hereditary spherocytosis. They were both in good health and neither had any significant past history of disease. Subject I 7 was dead; there was a history of jaundice while in the Army.

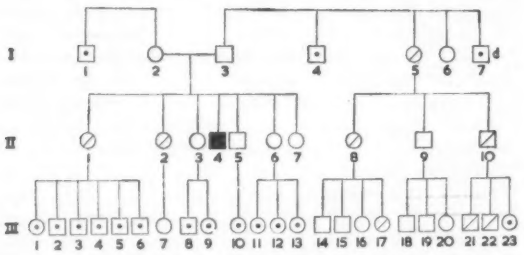

FIG. 1.—Pedigree of family. □ Normal male. ○ Normal female. ◪ and ⊘ Affected male and female respectively. ▫ and ⊙ Members not examined. The proband is represented by a black square.

Clinical and Laboratory Findings in the Family Studied

Subject	Sex and Age	Haemoglobin (g. 100 ml.)	P.C.V. (Wintrobe) %	Reticulocytes %	Spherocytes	Osmotic Fragility	Splenomegaly
I 2	F 64	14·4	45	1·4	–	Normal	–
I 3	M 68	14·6	44	1·6	–	,,	–
I 5	F 65	13·6	38	5·4	+	Increased	+
I 6	F 62	15·1	43	2·4	–	Normal	Not examined
II 1	F 35	13·6	40	10·0	+	Normal once; increased once	+
II 2	F 32	13·2	40	3·8	+	Increased	+
II 3	F 30	13·6	40	3·0	–	Normal	–
II 4	M 26	15·6	45	4·6	+	Increased	+
II 5	M 25	15·7	47	1·6	–	Normal	–
II 6	F 22	15·4	45	4·4	–	,,	–
II 7	F 20	15·0	46	1·0	–	,,	Not examined
II 8	F 45	14·3	46	1·5	–	Normal three times; increased once	–
II 9	M 44	15·1	46	1·1	–	Normal	–
II 10	M 33	16·6	45	3·5	+	Increased	+
III 7	F 7	12·6	38	1·6	–	Normal	–
III 14	M 21	15·7	49	0·2	–	,,	–
III 15	M 18	15·2	47	1·4	–	,,	–
III 16	F 16	15·0	45	0·8	–	,,	–
III 17	F 10	12·6	36	12·8	+	Increased	+
III 18	M 13	13·6	44	1·3	–	Normal	–
III 19	M 11	13·5	41	1·2	–	,,	–
III 20	F 7	12·8	39	0·6	–	,,	Not examined
III 21	M 11	13·3	39	2·1	+	Increased	+
III 22	M 9	12·3	37	3·7	+	,,	–

As it seemed likely that the father (Subject I 3) was indeed a carrier, he was re-examined with similar normal clinical and haematological findings. On this occasion the osmotic fragility of red cells incubated at 37° C. for 24 hours was determined and found to be normal. The curve for freshly drawn red cells is shown in Fig. 2 and for incubated cells in Fig. 3. This member has since died, and it was not possible to carry out further tests.

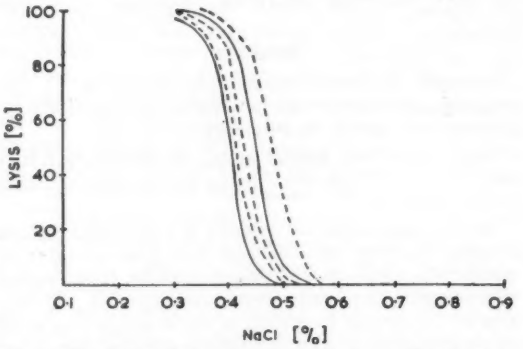

FIG. 2.—Osmotic fragility curves of freshly drawn blood. From left to right, the carrier father (Subject I 3); an affected cousin (Subject II 8) who showed an abnormal curve after repeated testing; the proband (Subject II 4).

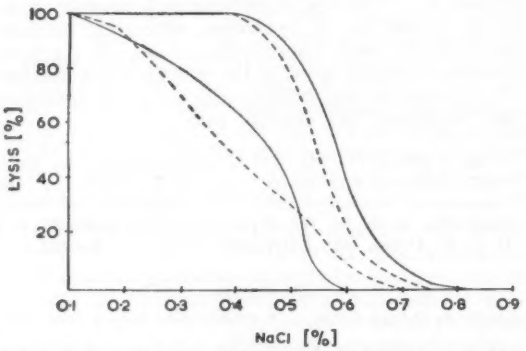

FIG. 3.—Osmotic fragility of incubated blood. From left to right, an affected cousin (Subject II 8) who subsequently showed increased osmotic fragility, and the carrier father (Subject I 3).

All the members of generation II were examined. Five, including the proband, were diagnosed eventually as suffering from hereditary spherocytosis. Subject II 1 was not anaemic and had no symptoms of ill-health. She showed splenomegaly, spherocytosis, and reticulocytosis. On the first examination the red-cell osmotic fragility was normal; when retested one year later the curve was just beyond the normal range (M.C.F. 0.455%). Subject II 2 was clearly affected, showing splenomegaly, spherocytosis, reticulocytosis, and increased red-cell osmotic fragility. There was a vague past history of anaemia in childhood, but the haemoglobin value was normal at the time of examination. Subject II 6 has not been included in the affected group, as, although she showed a reticulocyte count of 4.4%, there were no spherocytes present in the blood film, the osmotic fragility of the red cells was normal, and the spleen was not palpable. Subject II 8 was considered initially to be unaffected, even though she was the mother of an affected child. Laboratory findings representative of the first three examinations were haemoglobin 14.3 g./100 ml., haematocrit 46%, reticulocytes 1.5%, and absence of spherocytes in the stained blood film. Osmotic fragility of both fresh and incubated cells was normal (Figs. 2 and 3). She suffered

from menorrhagia, for which hysterectomy was performed. When re-examined some months later she showed 4% reticulocytosis and osmotic fragility of both fresh and incubated cells was definitely increased. Subject II 10 had spherocytosis, reticulocytosis, increased osmotic fragility, but no splenomegaly. He was not anaemic and had no symptoms of ill-health.

Ten members of generation III were examined. Three were diagnosed as suffering from hereditary spherocytosis. Subject III 17 showed reticulocytosis, spherocytosis, increased red-cell osmotic fragility, and splenomegaly. Her reticulocyte count was the highest recorded in this family study. She was recovering from a pyrexial illness at the time of examination. There was no anaemia or any significant past history. Subject III 21 showed splenomegaly, spherocytosis, and increased red-cell osmotic fragility. The reticulocyte count was 2.1% and there was no anaemia. He was stated to have been jaundiced at birth, but was a premature baby. Subject III 22 was considered by his mother to be delicate and was taking "blood tonics." He showed reticulocytosis, spherocytosis, and increased red-cell osmotic fragility. The spleen was not palpable and there was no anaemia.

Discussion

Nine of 24 members examined in this family appear to be suffering from hereditary spherocytosis, and one (Subject I 3) seems to have been a haematologically normal carrier. It is possible that further testing would have eventually detected an abnormality in this individual as it did in Subject II 8; he died from coronary occlusion while this study was in progress. With the exception of the proband, no subject was found to be anaemic, indicating the mild nature of the disease. The anaemia shown by the proband could have been accounted for by blood loss only, although it is also possible that he suffered from an "aplastic crisis" after the injury to his pelvis. Unfortunately, reticulocyte counts were not performed until the seventh day after the injury, at which time he showed reticulocytosis and the haemoglobin value was rising.

Seven of the eight subjects who showed spherocytosis had reticulocytosis greater than 3%. Subject III 21, who had spherocytosis, increased red-cell osmotic fragility, and splenomegaly, had a reticulocyte percentage of only 2.1%. The highest reticulocyte percentage (12.8) was shown by Subject III 17, who was recovering from an unexplained fever at the time of examination. Subject II 6 had 4.4% reticulocytes, but no other findings to suggest hereditary spherocytosis, and has not been included among the affected members.

Red-cell osmotic fragility was found to be abnormal in all nine affected members, but only on repeated testing in two of these (Subjects II 1 and II 8). It was of particular interest that initially the osmotic fragility of incubated red cells was normal in Subject II 8. The red cells showed mild hypochromia at this time due to menorrhagia. After hysterectomy the osmotic fragility of freshly drawn cells was definitely abnormal, as also was the fragility of incubated cells.

Splenomegaly was found in five subjects. In four the degree of enlargement was such as to be just detected clinically; Subject III 17 was found to have a firm enlargement of the spleen which extended 3 cm. below the left costal margin.

The family pedigree (Fig. 1) suggests transmission of the disease as an autosomal dominant characteristic, with variable expression of the affected gene. The family findings indicate the necessity for a full investigation when studying inheritance. The proband might have been considered an example of mutation if his parents only had been investigated; the same might have been said of Subject III 17 if repeated laboratory investigations had not demonstrated eventually the disorder in her mother.

The inheritance of mild hereditary spherocytosis appears the same as that for the classical disease. The similar severity of the clinical findings in affected members of this family suggest that the gene for hereditary spherocytosis may occur in allelomorphic form. In this family an iso-allele may be responsible for a mild disease. The other possibilities are that the condition described in this paper is a different one from typical hereditary spherocytosis, or that each affected member is revealing incomplete penetrance of the gene responsible for the typical disease. Both these possibilities appear unlikely.

The disease in this family is so mild that no treatment seems to be indicated.

Summary

A large family suffering from symptomless hereditary spherocytosis in three generations is described. The diagnosis was established in affected members on clinical and laboratory findings.

No haematological abnormality could be detected in one member who, on genetic grounds, was transmitting the disease. All ten members of the second generation were examined and five were found to be affected. In one affected member of this generation haematological abnormalities were detected only after repeated testing.

It is suggested that the gene responsible for hereditary spherocytosis occurs in allelomorphic form.

I would like to thank Dr. W. R. Pitney for criticism of the manuscript.

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The University of Nigeria occupies a large site at Nsukka, near Enugu in Eastern Nigeria, where accommodation has already been provided for over 270 students who came into residence on October 12. Princess ALEXANDRA performed the formal ceremony of laying the foundation stone during her visit to the recent Independence celebrations. The Senate of London University has agreed to enter into a tripartite association, for a period whose length is to be decided in due course, with Michigan State University and this new University. The new University will from the outset grant its own degrees, but will benefit from British and American assistance and advice both in its planning and in such matters as staffing and examining. The British contribution will come partly through the Inter-University Council, which will arrange a number of secondments to the new University, and partly through the University of London, whose role will be to advise on academic matters in association with Michigan State University, and to suggest the names of members of the University of London to be invited to serve on the council, to visit Nigeria, and to join boards of examiners. (*University of London Gazette*, October, 1960.)

RESCINNAMINE IN TREATMENT OF HYPERTENSION IN HOSPITAL CLINIC AND IN GENERAL PRACTICE*

BY

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Preparations of *Rauwolfia serpentina*, and in particular its alkaloid reserpine, are widely used in the treatment of hypertension. Their value has been challenged on the grounds that they rarely produce an adequate result in severe hypertension and that they can cause undesirable side-effects, especially depression.

Many workers feel that they still have a place in the management of less severe hypertension, and that the adoption of smaller dosage reduces significantly the risk of side-effects. It has been suggested that rescinnamine, another alkaloid of rauwolfia, might have an antihypertensive effect equal to that of reserpine, but with less tendency to cause depression.

The following report describes an experiment with two objectives: firstly, to determine whether the antihypertensive effect of reserpine on a group of patients might be equalled by a smaller dose of reserpine together with rescinnamine, and whether the combined regime might have fewer side-effects; and, secondly, to compare the conclusions of the hospital clinic with an independent assessment of the results in the same patients by their own family doctors, during the same period of time.

It was hoped also to obtain some data about the relationship between blood-pressure readings made in the hospital clinic and those made in the home or in the consulting-room.

Material and Methods

Nine general practitioners were invited to co-operate in this investigation. They were asked to select a few of their patients with moderate hypertension who might benefit from antihypertensive therapy and who would be able and willing to attend at regular intervals over a period of nine months. No strict limitations were applied to the choice of patients, but it was suggested that their "casual reading" at the time of selection should be not less than 180/100 mm. Hg, and that those with very severe hypertension should not be included because the design of the experiment required prolonged mild antihypertensive therapy, unlikely to be sufficient for them. By the criterion of greater severity used in previous publications from this department (Fife *et al.*, 1958, 1959)—namely, a mean diastolic pressure while on placebo therapy of 120 mm. Hg or over—only 4 of the 23 patients finally included would be regarded as severe cases; 16 were "milder" cases, and 3 would have been omitted as "too mild" because their mean diastolic pressure on placebo was under 100 mm. Hg.

The ages ranged from 47 to 72 years, with an average of 58. All but one were women. On an average they were thus older and had less severe hypertension than the groups of hypertensives previously studied by this unit.

The initial assessment included 12-lead electrocardiogram, radioscopy, and blood-urea estimation, and, in patients under 55 years of age, intravenous pyelography. By the usual criteria, all were considered to have hypertension of idiopathic type.

The patients attended hospital once a month at a time set aside for this purpose, and the general practitioners, so far as was possible, attended with their own patients and participated actively in the assessments and observations. Between the hospital visits the patients were attended by their own doctors weekly, and two independent records of blood-pressure readings were kept, one in the hospital clinic and the other for readings made at home or in the consulting-room.

The clinic blood-pressure readings consisted of six measurements at each visit, the first in the sitting position, the second and third in the recumbent position at 15 and 30 minutes respectively, and the last three at one-minute intervals in the standing position. The "home" or "consulting-room" readings consisted of two measurements at each visit, one in the recumbent position and one standing.

Therapy

The treatment consisted of three consecutive three-month courses of tablets, requiring a total attendance by each patient of nine months. The tablets were supplied in bottles labelled Regime 1, 2, and 3 respectively, and neither the patients nor the doctors knew which was which. One day's supply of the various regimes was as follows:

Regime 1: Reserpine 0.5 mg. + rescinnamine 1 mg.
Regime 2: Reserpine 1.5 mg.
Regime 3: Placebo.

Thirty-five patients began this experiment, but for various reasons 14 were excluded before it was completed. In order to avoid possible bias from the order in which the regimes were used, successive patients began with a different regime, so that approximately one-third of the patients had each of the regimes as their first.

In terms of the clinic blood-pressure readings, the result of a regime of therapy was calculated by subtracting the mean of the three sets of six readings made during that therapy from the corresponding mean pressure while on the placebo. Both systolic and diastolic pressures were examined, and the pressure reduction was calculated as a percentage of the placebo mean pressure.

TABLE I.—*Percentage Reduction in Systolic and Diastolic Pressures from the Two "Active" Regimes*

Percentage Reduction	Systolic				Diastolic			
	Regime 1		Regime 2		Regime 1		Regime 2	
	Clinic	Home	Clinic	Home	Clinic	Home	Clinic	Home
0–5	4	3	11	7	7	4	7	3
6–10	4	4	2	5	4	5	5	8
11–15	3	2	2	3	5	5	4	3
16–20	1	1	1	1	2	1	4	4
21–25	0	0	0	0	0	0	0	1
Rise in pressure	9	10	5	4	3	5	1	1
Total patients ..	21	20*	21	20*	21	20*	21	20*

* Home record of one patient inadequate—excluded.

*With the collaboration of Drs. G. Adam, J. B. Barr, J. H. Brown, J. Carnduff, A. A. Gordon, B. S. Hutchison, R. L. Low, G. S. P. Noble, and L. Reid.

To represent the home or consulting-room blood-pressure we had available for each regime of treatment from 8 to 12 sets of two blood-pressure readings; the average of all of these was taken, except for readings made within two weeks of commencing a new regime. The fall in pressure from the placebo level was calculated in the same way as for the clinic readings.

The reductions in pressure are summarized in Table I. If the clinic assessment is considered first, it is seen that the mild antihypertensive effect of reserpine in a dose of 1.5 mg. daily is again confirmed, and that this effect is greater on the diastolic pressure than on the systolic. Four of the 21 patients had a fall in mean diastolic pressure of 16% or more, but only one achieved such a fall in systolic pressure.

The combination of reserpine 0.5 mg. and rescinnamine 1 mg. daily appeared to be slightly less effective than reserpine 1.5 mg. daily; indeed, in the case of the systolic pressure there was a rise in almost as many patients as there was a fall. The effect of this combination of drugs on the diastolic pressure was a little more convincing, but in only 2 of the 21 patients was the pressure reduction 16% or over, which one might reasonably require for a "clinically useful" response.

Turning now to the home or consulting-room results, we see that very similar conclusions may be reached from them. Five of 20 patients had a fall in diastolic pressure on reserpine alone of 16% or over, as compared with one patient on the combined regime. The effects on systolic pressure were again of less degree, and only one patient had a clinically useful reduction of systolic pressure from each regime.

In brief, the results of both assessments suggest that a combination of reserpine 0.5 mg. daily and rescinnamine 1 mg. daily has a mild antihypertensive action similar to but probably less than that of reserpine alone in a dose of 1.5 mg. daily.

It is important to know also whether the combined regime had a lower toxicity than reserpine alone. The difficulty of ascertaining that in clinical trials of this type is shown in Table II, which lists the frequency of

TABLE II.—*Symptoms Complained of During the Three Regimes*

Symptom	Regime 1	Regime 2	Regime 3
Tiredness, lethargy	5	9	5
Drowsiness	1	4	
Depression	1	3	6
Nervousness		4	5
Weakness	1		
Insomnia		1	1
Dyspepsia, nausea	2	1	1
Headache	2	1	6
Lightheadedness	4		
Chest pain	3	3	3
Dyspnoea		2	
Palpitation			1
Salty taste		1	1

symptoms complained of while on the various regimes, including the placebo, whether these were thought to arise from the drugs or not. The rather high incidence of a number of symptoms, such as depression, nervousness, and tiredness, during the placebo regime suggests that one should be cautious about making too many deductions about the effect of the active drugs in producing these symptoms. One might be justified in thinking, however, that the bigger dose of reserpine had a greater tendency to produce sleepiness or lethargy than the smaller dose of reserpine along with rescinnamine. The frequency of depression during the placebo regime in the present series makes it impossible to draw any valid conclusions about the relative merits of the other two regimes in terms of this side-effect.

Discussion

While preparations of *Rauwolfia serpentina* are in common use in the clinical management of hypertension, their value, particularly in severe hypertension, has been questioned (Turner, 1959). The alkaloid reserpine, which has had the widest use, is known to produce depression as a side-effect in a proportion of cases, and although this is less often seen with the smaller dosages now favoured for its use in hypertension, the depression may occasionally be severe. Numerous other alkaloids of rauwolfia have been isolated and several are now in clinical use.

Rescinnamine was isolated and identified chemically by Klohs *et al.* (1954), and its pharmacology was described by Cronheim *et al.* (1954). Its hypotensive effect in dogs was found by Cronheim and Toekes (1955) to be greater than that of reserpine. From a clinical trial in human hypertension, Smirk and McQueen (1955) reported that there was no important difference between the hypotensive effects of rescinnamine and those of reserpine. They found that certain mental symptoms, such as depression, occurring during reserpine therapy might often by relieved by changing to rescinnamine; but other patients complained of tenseness, anorexia, and abdominal discomfort from rescinnamine. Smirk and McQueen used reserpine in a dose of 0.5 to 1.5 mg. a day, and rescinnamine in the same dosage; and they noted that some patients could tolerate a much larger dose of rescinnamine. Moyer *et al.* (1955) found that rescinnamine in a dose of 2–4 mg. daily was as effective in the reduction of blood-pressure as reserpine, though sometimes less severe; and the findings of Herschberger *et al.* (1956) and of Winton (1957) were essentially similar. On the other hand, Lemieux *et al.* (1956) found that on a weight-for-weight basis rescinnamine was a less potent alkaloid than reserpine, and that a dose of 1–2 mg. daily did not have a significant antihypertensive effect.

Our own results suggest that the antihypertensive effect of rescinnamine 1 mg. daily along with reserpine 0.5 mg. daily is similar to that of reserpine 1.5 mg. daily in respect of a greater effect on diastolic than on systolic pressure, but that it is less in degree than that of reserpine alone in a dose of 1.5 mg. daily. This agrees with the view of Lemieux *et al.*, that, dose for dose, rescinnamine is less potent than reserpine in the therapy of human hypertension.

As regards side-effects, our results were consistent with the view that, in the same dosage, rescinnamine may be slightly less toxic than reserpine, but, in view of the high incidence of similar symptoms in this group of patients while having the placebo, we cannot comment in more definite terms on that aspect.

The evidence of this experiment does not suggest that rescinnamine is likely to offer any substantial advantage over reserpine in the treatment of hypertension.

Collaboration with Family Doctors

It has long been taught that general practice is a fertile field for clinical observation and research. The increasing specialization in hospital practice, and the growth of elaborate techniques of investigation, have perhaps tended to discourage attempts at fundamental

research in general practice, and shortage of time and other factors make even simple clinical investigations difficult to undertake.

In recent years Mackintosh (1954), Fry (1958), and other writers have felt that co-operation between hospital out-patient departments and family doctors should make possible certain types of clinical investigation that would be difficult for either to accomplish alone.

One field in which a combined approach seems worth considering is the clinical assessment of some of the numerous new drugs now available. There are many difficulties in the way of a controlled clinical trial of a drug in general practice. Ethical considerations are involved, and our experience is that patients are more willing, and even keen, to participate in an experiment involving new remedies when it is carried out under the guidance of a hospital clinic with special experience in that field. On the other hand, it is desirable of most remedies that they should be effective and practicable for use in general practice, and it would be helpful if methods of assessment could be devised which were known to give similar results under hospital and general practice conditions.

It is perhaps unnecessary to emphasize that such investigations must be planned in detail in advance, and that a certain sacrifice of time by the participants is inevitable. Where subjective responses of patients are being assessed, or where objective changes of minor degree may be significant, current practice demands that bias of both patient and physician be minimized by the use of the double-blind technique.

This paper describes a simultaneous controlled clinical trial in the hospital out-patient department and in general practice of the effect of certain regimes of treatment for hypertension. On the whole the results of the two assessments show a remarkable agreement.

The tabulated blood-pressure readings were studied to find whether there was any general trend to higher readings in one or other assessment. There is no doubt that a single estimation of blood-pressure at a diagnostic consultation in hospital often gives a much higher reading than the usual level recorded by the family doctor. Yet in this investigation the blood-pressure readings during placebo therapy did not show any general tendency to higher readings at hospital.

In a few subjects there was a substantial and consistent discrepancy between the two sets of readings —for example, Case 5 showed much higher readings in hospital throughout the whole period, and Cases 8 and 15 the converse, particularly for systolic pressure. These facts, and the rather wide scatter of individual readings, indicate once more the need for a fairly large number of blood-pressure recordings in each phase of such an investigation. And it is clear that a smaller number of patients would be unlikely to give a conclusive result.

Simple investigations of this kind, involving close co-operation between hospital and family doctors, can be educative to both and may produce useful information.

Summary

A controlled clinical trial is described comparing reserpine with a smaller dose of reserpine plus rescinnamine in hypertension.

The results were assessed independently at the hospital clinic and by the patients' family doctors, working in co-operation.

Rescinnamine is unlikely to offer any useful advantage over reserpine in the treatment of hypertension.

Clinical investigations involving co-operation between hospital and family doctors have possibilities that should be explored further.

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MONOPLEGIA AND HORNER'S SYNDROME FROM PRESSURE PALSY

REPORT OF A CASE AND ANATOMICAL DISCUSSION

BY

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Transient paralyses of the median and ulnar nerves sustained by prolonged pressure during narcotic-induced sleep, and particularly after bouts of acute alcoholism, are relatively commonly observed occurrences. Likewise, the condition of "Saturday night paralysis," involving the radial nerve in the upper part of the arm, is a well-known clinical entity. But, as Walshe (1958) points out, it is rare for the nerve of a healthy subject to sustain such pressure palsy, the majority of such patients being chronic alcoholics with an already debilitated peripheral nervous system.

The majority of brachial-plexus-pressure palsies reported in the literature are cases sustained during anaesthesia. Wood-Smith (1952) describes a lesion of C 5 and C 6 roots sustained during operation, and cases are also reported by Raffan (1950), Shaw (1953), and Westin (1954). The *Lancet* (1950) had a leading article on this subject; and, in particular, the hazards of the Trendelenburg position have been well covered. Ewing (1950) stressed the mechanism of abduction of the arm in the Trendelenburg position, causing traction injuries. Traction was incriminated also in the earlier series of Clausen (1942). Kiloh (1950) felt that both traction and pressure were of significance. But reports of cases arising apart from operative anaesthetic hazard are few and far between; the case of "pack palsy" reported by Bom (1953) in the Korean war is a rarity.

The occurrence, therefore, of an extensive lesion of the cervical and brachial plexus due to direct pressure

in the neck is of some rarity, as well as providing an interesting illustration of the anatomy of the region. Such a case is reported below.

Case Report

A married woman aged 39 was admitted to Lancaster Moor Hospital in December, 1959, after an attempt at suicide by coal-gas poisoning. The psychiatric history being largely irrelevant to the present consideration, it is not discussed in detail, but it is of interest to note that, in association with an anxiety-depression of some months' standing, the patient had anorexia, and had lost a good deal of weight, being only 6 st. 9 lb. (42.2 kg.) on admission. She was of slim build, and had a somewhat drooping shoulder-girdle. Details of the suicidal attempt were not available at the time of admission, but routine physical examination revealed an almost complete monoplegia involving the left arm; anaesthesia, partial or complete, involving the cutaneous distribution of all the cervical nerves, including the brachial plexus; and left Horner's syndrome. The detailed physical findings were as follows.

Motor Lesion.—Slight movement of the fingers and a little flexion at the wrist were possible, but no active movement of extension of the wrist or fingers, no pronation-supination movement, and no flexion-extension at the elbow. Little movement of the shoulder-joint itself could be made, but the shoulder-girdle could be raised by the trapezius; there was some activity in the pectorals, and the rhomboids and serratus anterior were intact. All the tendon reflexes of the upper limb were abolished.

Sensory Lesion.—There was diminished sensation to pain and touch over the back of the head, the side of the neck extending just over the angle of the jaw, and the whole of the arm. Sensation was unimpaired over the pectoral region, and the lines of demarcation along the angle of the jaw superiorly and the clavicular region inferiorly were clearly indicated. The demarcation in the midline of the neck was fairly distinct, but over the parietal and occipital scalp the borderlines of sensory impairment were not so precise. Subjective paraesthesiae described as "tingling numbness" were felt over the head and neck on the affected side, but the limb was described merely as "numb."

Autonomic Lesion.—There was meiosis of the left pupil, slight ptosis, and dryness of the skin. Enophthalmos was not apparent.

Local Examination of Neck.—This revealed a small, slightly tender, firm, immobile, but not very discrete swelling at the posterior border of the sternomastoid at about the mid-point, and apparently arising from the substance of, or from beneath, that structure.

Discussion with the patient and her husband revealed that she went to put the kettle on at 9.30 a.m. On an impulse she did not light the gas, and her husband found her at 12.30 p.m. in the gas-filled kitchen, slumped unconscious with her neck over the hard back of a chair. He found her neck red and swollen along the line of contact. The subject in the accompanying illustration shows the position in which the patient was found.

By next day the sensory loss had almost entirely recovered, although some paraesthesiae were still complained of. Considerable motor recovery had occurred, the flexors and extensors of the wrist and fingers having regained full power, and there being some function of extension at the elbow. There was still, however, complete loss of power in the biceps and supinator, and in the deltoid, supraspinatus, and infraspinatus; and Horner's syndrome was unaltered.

Treatment was instituted with passive and active movements and galvanism. Further improvement was slower, and when the case was last reviewed there was still a complete palsy of the deltoid and spinati. The progress of the clinical picture is summarized in the Table.

Summary of Clinical Progress

	On Admission	Next Day	After 2 Weeks	After 5 Weeks
Deltoid	0	0	0	0
Supraspinatus	0	0	0	0
Infraspinatus	0	0	0	2
Biceps	0	0	3	5
Supinator	0	0	0	5
Triceps	0	4	4	5
Pectorals	2	4	4	5
Flexors of wrist and fingers	2	5	5	5
Extensors of wrist and fingers	0	5	5	5
Sensory impairment	Present	Doubtful	Absent	Absent
Horner's syndrome	,,	Present	Not noted	,,

The grading of muscle power numbered 0-5 is that recommended by the Medical Research Council: 0 = Complete paralysis. 1 = Flicker of voluntary action. 2 = Sufficient to move joint. 3 = Action against gravity. 4 = Action against gravity and resistance. 5 = Full power.

Discussion

In the position in which the lesion was sustained, the adducted left arm exaggerated the depression of the shoulder-girdle in this patient, who was already of asthenic "drooping" stature. A period of anorexia resulting in loss of weight meant that there was very little superficial fascia protecting the structures in the posterior triangle of the neck. These factors would approximate even more closely the crowding together of the three trunks of the brachial plexus before the ramification to form the cords occurs, and would tend to drag the trunks out from their protected site between the scalenus anterior and the scalenus medius. An injury at this site would explain the sparing of the longitudinal cervical musculature, the serratus anterior, rhomboids, and phrenic contribution (all derived from *roots* of the plexus) while involving the suprascapular (derived from the upper *trunk* of the plexus) and all the branches of the plexus below the trunks. The presence of the swelling at the posterior border of the sterno-mastoid overlying this point would suggest that this was the site of maximum injury.

Emerging more superficially, but still at approximately the same site at the mid-point of the posterior border of the sterno-mastoid, a spray of cutaneous nerves spreads out fanwise—the three supraclaviculars, the anterior cutaneous of neck, and the greater auricular. The lesser occipital is exposed a little higher, but in a linear lesion it is understandable how all of these might be affected. This area also corresponds to one of the "trigger points" illustrated by Reichert (1955), which may account for some of the initial diffuse paraesthesiae described.

It is not quite so easy to appreciate how the cutaneous sensation of the occiput comes to be involved, since this is supplied by the greater occipital nerve from the posterior primary ramus of C 2. However, the sensory

loss of this area was not so well defined, and, in any case, there are known to be filamentous connexions between the greater and the lesser occipital nerves, the latter being derived from the anterior primary ramus of the same segment. Again, another possibility is direct involvement, since, as Wright and Brady (1958) point out, the greater occipital nerve rests on the vertebral arch of the axis, in a vulnerable position, unprotected by an intervertebral foramen.

Deep and internal to the swelling found in this case is the site of the superior cervical ganglion of the sympathetic system, lying on the lower part of the longus capitis muscle. It is suggested that pressure on this structure was responsible for Horner's syndrome, thus completing the clinical picture observed.

Remembering that the patient was breathing a proportion of carbon monoxide for a period of three hours, we are justified in assuming that there was a neurotoxic element at work lowering the threshold for neuronal damage for the more direct factors at work.

Summary

A case is described of an extensive cervical and brachial plexus injury arising as a result of linear pressure on the neck during a coma produced by coal-gas in the course of a suicidal attempt. It is noted that most of the literature on pressure palsies of the brachial plexus is concerned with cases sustained as an operative anaesthetic hazard.

An attempt is made to correlate the clinical findings with the regional anatomy. The posture and habitus of the patient appeared to be of contributory significance, as well as the mode of suicidal attempt.

I wish to thank Dr. Stanley Smith for permission to publish details of this case, and Dr. F. Hillman for the photograph.

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"The progess which the Elderly Invalids' Fund has made year by year was well maintained in 1959. A total of 135 invalids received financial assistance compared with 92 in 1958. As this increase in the number of patients could have been achieved simply by helping more temporary cases and fewer permanent ones, the better way of measuring the progress is in terms of patient weeks, which amounted to 2,086 in 1959 compared with 1,290 in 1958. This is equivalent to supporting 40 invalids throughout the year compared with 25 in 1958. Unfortunately, we cannot show a proportionate increase in our income, with the result that this increased work and commitments have caused us a deficit of £387 9s. 3d. . . . Expenditure during the year amounted to £5,205 compared with £4,850 in 1958. Income at £4,817 was £182 less than the previous year. . . . Attention can again be drawn to the low administrative costs—£115. There is still no paid staff and expenses are only for printing, stationery, and postage. These have cost more than in 1958, but with increasing work the use of more writing paper, envelopes, and stamps is inevitable." (*Elderly Invalids' Fund Annual Report, 1959*).

POST-MORTEM SERUM CHOLESTEROL LEVELS

BY

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It has been shown that there is a higher serum cholesterol associated with coronary artery disease (Oliver and Boyd, 1953 ; Dock, 1958), and its estimation is a recognized procedure in patients with this condition.

The purpose of this investigation was to discover if the level of the serum cholesterol altered after death. If it could be established that hours or even days after death the serum cholesterol had not altered appreciably from the level just before or at death it was thought that post-mortem estimation could be taken to indicate the serum cholesterol during life and could perhaps be used in the correlation of serum cholesterol levels and the state of the arteries as found at necropsy.

Method

Two preliminary observations were made. Firstly, blood taken from patients by venepuncture was divided into two parts and the serum cholesterol level estimated on one part while the second sample was left for four days in the specimen refrigerator at a temperature of 5° C., and a second cholesterol estimation was performed. No significant difference was found between the two results (Table I). Secondly, it had been

TABLE I

Specimen	Original Serum Cholesterol (mg./100 ml.)	Serum Cholesterol Level After 4 days (mg./100 ml.)
1	165	160
2	203	210
3	122	117
4	118	110
5	392	403
6	372	362
7	247	243
8	366	363
9	207	204
10	250	254
11	216	219
12	199	201

found that when samples of blood taken at post-mortem examination were cultured the majority in varying degrees grew *Escherichia coli* and "coliforms." Blood of known cholesterol content was therefore inoculated with these organisms and kept for the remainder of the time in the post-mortem room refrigerator at 5° C.

At 48 hours and after six days the cholesterol was again estimated, and there was found to be no significant change (Table II).

TABLE II

Specimen	Original Serum Cholesterol Level (mg./100 ml.)	48 Hours After Inoculation (mg./100 ml.)	6 Days After Inoculation (mg./100 ml.)
1	156	152	151
2	192	169	167
3	179	167	167
4	125	109	105
5	337	348	345
6	158	148	155
7	168	162	154
8	112	108	109
9	380	363	360
10	343	339	331
11	423	420	418
12	381	373	367

As the levels did not appreciably change the following procedures were undertaken. Blood samples were taken from very ill patients and the serum cholesterol levels estimated. If in any case death did not occur within 24 hours the blood was discarded and a fresh specimen taken. In one case blood was taken just after death.

Bodies were left at a temperature of +5° C. in the post-mortem room and at varying times blood samples were taken. This sampling presented no difficulty: a 20-ml. syringe and a 5-in. (12.5 cm.) No. 14 gauge needle was used to take the blood from a femoral vein or artery, from the heart by substernal puncture, or direct from the heart at necropsy. There was usually a great deal of haemolysis, but by long centrifugation enough serum was always obtained.

The estimations were performed by the colorimetric method of Sackett (1925).

The results (Table III) in 26 cases show that up to 60 hours after death there is no large fluctuation in the cholesterol estimation, and in two cases at 90 hours after death the level was quite near that found before death.

TABLE III

Age	Disease or Injury	Hours before Death Sample Taken	Cholesterol (mg./100 ml.)	Cholesterol (mg./100 ml.) Hours after Death			
				0–30	30–60	60–90	90+
21	Subarachnoid haemorrhage	18	187	190			
60	Crush injuries ..	19	139	137	134		
51	Cerebral haemorrhage	22	362	348			
56	Bronchopneumonia	23	90		91		
50	Subarachnoid haemorrhage	16	221		250		
74	Steatorrhoea ..	12	37		48		
41	Chronic nephritis ..	12	113		112		
9	Influenza	1	82	81			
32	Cerebral haemorrhage with hypertension	8	231		214		
60	Neoplasm pancreas	12	89		80		
46	Subarachnoid haemorrhage	18	362	379			
28	Multiple injuries ..	1	146	148			
69	Influenza	7	208	218	187		195
39	Fractured skull ..	At death	116		125		
68	Pneumonia	,,	53		58		
66	Influenza	6	76		76		
24	Carcinoma of bladder	At death	187				183
2	Carcinoma of prostate	2 hours after death	147		157		
68	Cerebral haemorrhage	8	234		241		
61	Pulmonary abscess	At death	42		46		
61	Cor pulmonale ..	,,	88			96	
70	Mesenteric thrombosis	3	95		94		
38	Multiple injuries ..	½	110		108		
54	Cor pulmonale ..	9	83		86		
53	Cerebral haemorrhage	6	138	135	132		
60	Nephrotic nephritis	3	620	620			

Summary

The serum cholesterol was estimated on 26 patients shortly before and at varying times after death. The ante-mortem and post-mortem levels were close.

The post-mortem serum cholesterol may be taken as an indication of the level just before death.

I thank Dr. A. J. Thomas and Dr. C. R. E. Freezer for their interest and help, and Mr. Christopher, of East Glamorgan Hospital, for his assistance with the cholesterol estimations.

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RAPID METHOD FOR ESTIMATION OF CARBON MONOXIDE IN BLOOD

BY

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A simple, rapid, and accurate method of measuring the carbon monoxide content of blood is required for investigation of subjects exposed to that gas. Analysis of alveolar gas which has reached equilibrium with the pulmonary capillary blood (Sjöstrand, 1948) is simple and accurate but time-consuming. This paper describes a rapid method based on Sjöstrand's method and compares its accuracy with the results of direct blood-gas analysis.

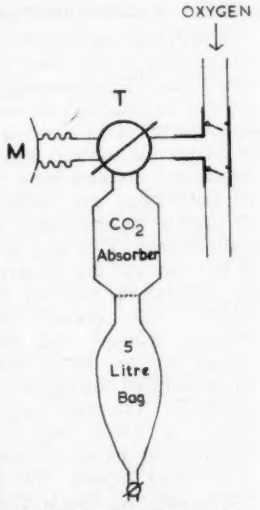

FIG. 1.—Breathing circuit. The mouthpiece (M) is fixed to a three-way tap (T) which can be turned so that the subject first washes out his lungs with oxygen and then rebreathes from the 5-litre bag through the CO_2 absorber.

Method

The subjects were six healthy adults (five male and one female) aged 26 to 34 years, and the procedure was as follows:

Each subject washed out the nitrogen from his lungs by breathing 100% oxygen from a simple open circuit (Fig. 1) for a period of three minutes. At the end of this time he was instructed to take a maximum inspiration and hold his breath. The three-way tap (T) was then turned and he exhaled through a carbon dioxide absorber, previously washed out with oxygen, into an empty bag and rebreathed from this bag for a further three minutes. The contents of the bag were then analysed for oxygen by the Haldane method and for carbon monoxide, using an infra-red meter. From these figures the basal blood carboxyhaemoglobin saturation (COHb%) was calculated, using Dahlström's (1955) equation, namely:

$$COHb\% = \frac{M \times 100 \times p_{CO}}{p_{O_2} + (M \times p_{CO})}$$

where $M = 231$ and p_{CO} and p_{O_2} are the partial pressures of carbon monoxide and oxygen in the equilibrated bag.

During the last minute of the rebreathing period 7 ml. of venous blood was withdrawn for the direct measurement of the carbon monoxide content of the blood by the method of Lawther and Apthorp (1955). The oxygen capacity of the blood of each subject was measured by the method of Van Slyke, and from these

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measurements the percentage of haemoglobin saturated with carbon monoxide was calculated.

Each subject was given carbon monoxide in air to breathe at approximately half-hourly intervals in quantities sufficient to raise the blood carbon monoxide level step-wise from the initial level to 20% saturation. At each level the carbon monoxide saturation was measured by the rebreathing method and by simultaneous direct blood-gas analysis.

Results and Discussion

A scatter diagram (Fig. 2) shows there is close agreement between the carbon monoxide saturation measured by both methods within the observed range of 0 to 20% saturation. All but two points fell within the lines which represent differences of ±10%. In a subject whose haemoglobin concentration is normal (14.8 g./100 ml.) and is 20% saturation with carbon monoxide, these lines represent a difference of 0.4 volumes of carbon monoxide per 100 ml. of blood.

Analysis of the oxygen content of the rebreathed gas in the bag is the most time-consuming part of the estimation. The possibility that this analysis could be avoided by assuming the oxygen content of the bag was investigated. One hundred estimations of the COHb% of 14 normal subjects and 32 patients with cardiac or respiratory diseases were made by the method. The intrapulmonary gas-mixing efficiency was measured in all subjects by the helium closed-circuit method (Bates and Christie, 1950), as it is in patients with impairment of this function that variations in the oxygen content of the rebreathed bag are most likely to occur. The subjects were divided into three groups: normal subjects, patients with normal intrapulmonary gas-mixing (50 to 100%) (group 1), and patients with impairment of intrapulmonary gas-mixing (0 to 50%) (group 2). The results are shown in the accompanying Table. It will be seen that there was no significant difference in the oxygen content of the rebreathed bag in the three groups. The average oxygen content was 92.7% and the standard deviation of this figure was ±3.4%.

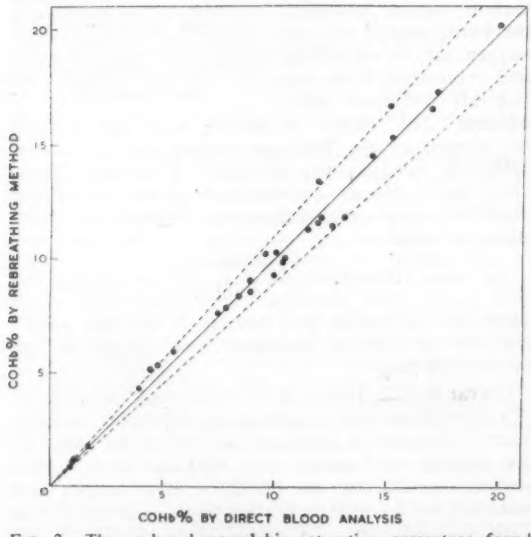

FIG. 2.—The carboxyhaemoglobin saturation percentage found by the rebreathing method described is plotted against that found by direct blood-gas analysis. The solid line indicates equality and the interrupted lines a difference between the methods of ±10%.

Mean Concentration of Oxygen in the Rebreathing Bag During 100 Estimations of Carboxyhaemoglobin by the Rebreathing Method

Group	No. of Subjects	Helium-mixing Efficiency		No. of Observations	Mean Oxygen %	Standard Deviation
		Range	Mean			
Normal subjects ..	14	50 to 100%	84%	62	92·4	±4·0%
Patients group 1 ..	22	50 to 100%	71%	22	93·6	±2·3%
,, ,, 2 ..	10	0 to 50%	32%	16	92·6	±1·9%
All subjects ..	46	—	—	100	92·7	±3·4%

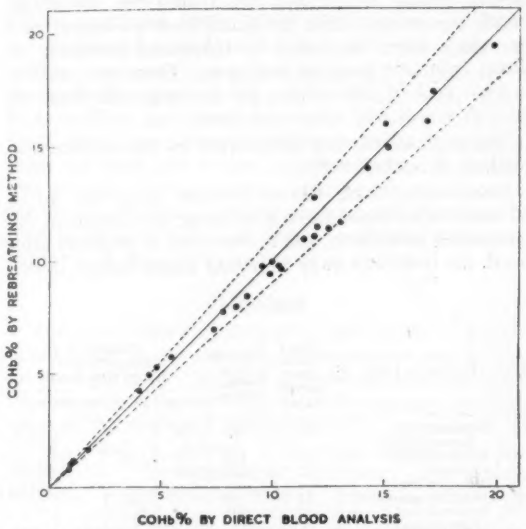

FIG. 3.—Scatter diagram identical to Fig. 2, except that the results of the rebreathing method have been recalculated, substituting a standard figure of 92% for the oxygen content of the rebreathed gas.

In view of these findings the 30 COHb saturations already described were recalculated, using in the equation a standard figure of 92% to represent the oxygen content of the rebreathed gas. On a similar scatter diagram (Fig. 3) these revised values all fell within the same limits as those originally described. It appears that the estimation of blood COHb% by the modified Sjöstrand method is as accurate as direct measurement of COHb in blood. For clinical and field studies it is apparently unnecessary to measure the oxygen content of the rebreathed gas. No patient experienced difficulty in carrying out the method.

Summary

A rapid modification of the Sjöstrand rebreathing method for the estimation of COHb% in blood is described and compared with direct blood analysis.

The modified rebreathing method gave results which agree well with those produced by direct blood analysis. Evidence is given which suggests that for routine purposes an assumed oxygen value can be used in Dahlström's equation.

We thank Miss Jane Howard for technical assistance, Mr. R. E. Waller for statistical analysis of the results, and Dr. P. J. Lawther for helpful advice.

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Medical Memoranda

Total Necrosis of Gall-Bladder After Emphysematous Cholecystitis : Recovery

Emphysematous cholecystitis resulting from infection by gas-forming organisms is rare, but has been reported by a number of authors. The literature on the subject was reviewed by Wilson (1957), who added a further case. The following case is recorded because of the unusual complication of total necrosis of the gall-bladder, with recovery of the patient.

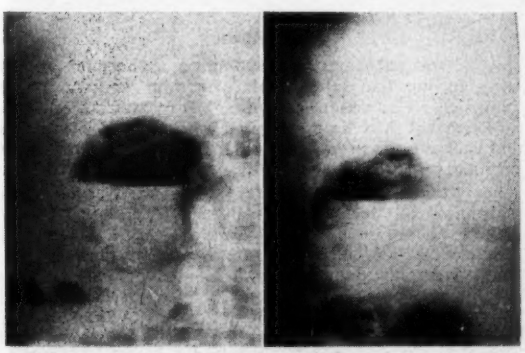
CASE REPORT

A man aged 52 was admitted to hospital on January 29, 1959. One week before admission, while travelling home, he suddenly had a severe pain under the right costal margin, lasting a few minutes. He had another similar attack the same evening, and vomited several times. Since then he had had continuous pain with exacerbation, had sweated profusely, and had lost his appetite. He thought his urine had been darker, but had noticed no jaundice. His doctor treated him as a case of cholecystitis, but, as his condition did not improve, referred him to hospital.

Four years previously a Polya partial gastrectomy had been carried out for a chronic duodenal ulcer. No abnormality of the gall-bladder was noted at laparotomy. For 10 years prior to this operation he had suffered from severe dyspepsia, which had not responded to medical treatment. Since then, however, he had been in good health until the present episode.

On examination the patient appeared ill, and was perspiring profusely. No jaundice was present. The temperature was 101° F. (38.3° C.), and pulse rate 100. The tongue was furred and halitosis present. Respiratory system —at the right base the percussion note was impaired, and the breath sounds were diminished. The cardiovascular system was normal. Abdomen: there was a ventral hernia through the old right upper paramedian scar; a tender, smooth mass with a rounded lower edge was palpable in the right hypochondrium and moved with respiration. The urine contained no bile. The white-cell count was 14,600, with 79% polymorphs. *X*-ray examination of the abdomen (see Fig.) showed a fluid level in the right upper quadrant. Outlining this, and more obviously seen below it, was a crescentic air shadow, and in the lateral view further air shadows could be seen in the region of the gall-bladder. The right side of the diaphragm was raised.

From the history, physical signs, and radiological findings, a diagnosis of emphysematous cholecystitis was made. The patient was treated by gastric aspiration, intravenous fluids, and a course of parenteral penicillin, combined with tetracycline orally. Over a period of 48 hours 22 ml. of polyvalent anti-gas-gangrene serum was given. A striking improvement in the patient's general condition followed, and within five days his pyrexia and tachycardia had subsided and his pain had disappeared. The abdominal mass became smaller, and was no longer palpable when he was discharged, 17 days after admission. Serial *x*-ray films also showed resolution of the gas shadows. At his next attendance in the out-patient department he complained of bouts of abdominal pain in the right hypochondrium. A cholecystogram did not outline the gall-bladder after a double dose of dye.



Fluid level in gall-bladder and surrounding crescentic air shadow (antero-posterior and lateral views).

A month after his previous admission he was readmitted for cholecystectomy. On March 10 laparotomy was done through a Kocher incision. A firm mass, the size of a tangerine, was found occupying the gall-bladder fossa, and this consisted mainly of omentum and fibrous tissue surrounded by dense adhesions. The gall-bladder had completely disappeared, but digital exploration revealed a small abscess cavity containing a few millilitres of creamy-coloured pus. Lying free in the centre of this cavity was a large slough which was evacuated. Further exploration with a large-bore needle revealed no further pus or bile, and no stone was felt in this mass. The abscess cavity was drained and the abdomen closed. The patient made an uneventful recovery. Culture of the pus grew only a few colonies of pneumococci.

COMMENT

It has long been recognized that gas-forming organisms of the *Clostridium welchii* group may be present in the bile or wall of an infected gall-bladder. Gordon-Taylor and Whitby (1932) showed that these organisms can be cultured in as high a proportion as 20% from the wall of gall-bladders with cholecystitis. Emphysematous cholecystitis is, however, rarely reported, and Wilson (1958) could find only one previous case in the British literature in reviewing 26 cases. He suggested that infection by anaerobic gas-forming organisms is secondary to the more common type of acute cholecystitis, and this would be in keeping with the fact that many cases, including the case presented here, have a relatively long history. Obstruction to the cystic duct is the precipitating factor, and in this case was probably due to adhesions around the duodenal stump resulting from the partial gastrectomy, as no gall-stones were found.

Though the diagnosis can be suspected from the general appearance of the patient, who looks more ill than would be expected, it depends for confirmation on the radiological findings. These are characteristic and were first described by Hegner (1931). The crescentic air shadow outlining the gall-bladder is due to gas in or just outside the wall of the gall-bladder as a result of patchy or, as in this case, complete sloughing of the wall. Diagnosis is of more than academic interest, as it influences treatment. Because of the danger of spreading gas-gangrene in the peritoneum or abdominal wall, treatment should be conservative in the acute phase. The use of antibiotics has resulted in an increasingly large proportion of cases responding to conservative measures. The ability to localize infection even when, as in this case, complete necrosis of the gall-bladder has occurred was strikingly demonstrated. It is impossible to assess the relative value of polyvalent anti-gas-gangrene serum, but on theoretical grounds it would seem to be worth using in conjunction with antibiotics.

The occurrence of gas-gangrene of the peritoneal cavity and abdominal wall as a rare complication of

elective cholecystectomy should also be borne in mind (Elliot-Smith and Ellis, 1957; Quinn, Lord, and Wade, 1942), as treatment, in order to be effective, must be promptly instituted.

I thank Mr. E. C. B. Butler, under whose care this patient was treated, for permission to publish this case.

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A Case of Intrauterine Osteogenesis Imperfecta*

Osteogenesis imperfecta is a rare disorder. It is characterized by fragility of the bones, which leads to the occurrence of multiple fractures. According to Watson-Jones (1952), accounts of this disease may be traced as far back as 1700. Vrolik in 1846 (quoted by Snapper, 1949) is believed to be the first to have reported a case of "fragilitas ossium" at birth. He called it "osteogenesis imperfecta." Looser (1906) distinguished between congenital and late forms. The congenital form (osteogenesis imperfecta congenita, or Vrolik's disease) is usually more severe, and multiple fractures may be found in the newborn child. It may even be possible to diagnose it *in utero*. Both prenatal and foetal types of this disease are recognized (Fairbank, 1951). Multiple bone fractures, excessive hyperplastic callus, and the formation of false joints while the foetus is *in utero*, all demonstrate that the disease is well advanced before birth. In addition to changes in long bones there are also changes in the skull due to defective ossification of the cranial bones, which in typical cases have the appearance of a jigsaw puzzle owing to the fact that they are largely made up of wormian bones (Teall, 1934). In such cases they are readily recognized on prenatal *x*-ray films.

It is almost impossible to give the incidence of this condition. Gain and Lawson (1952a, 1952b) encountered one case of this disease in 7,951 deliveries conducted between February, 1944, and June, 1951, at the Memorial Hospital at Phoenix. The baby was delivered spontaneously. It cried when touched or moved. There were multiple fractures of the legs and arms. The membrane bone of the skull was defective in formation. There was no blue sclera of the eyes. The child died of atelectasis on the sixteenth day. Commenting on the case, reported by these authors, the editor of *Obstetric and Gynaecological Survey* remarked that he had met with one case in 30,000 deliveries.

Posner and Goldman (1957) encountered only one case at the Bronx Hospital in a total of 40,000 deliveries. That case is very remarkable in that they made a prenatal diagnosis. The patient, a 27-year-old 3-gravida 2-para, was admitted at full term with mild labour pains. A breech presentation was recognized, and therefore pelvimetry studies were undertaken. The following abnormalities of the foetal skeleton were recognized on the *x*-ray film: deformity of the ribs due to multiple healed fractures, fracture of mid-femoral shaft with abundant callus, and apparent pseudo-arthrosis in the right lower quadrant; angulation deformity of the lower aspect of the femoral shaft secondary to previous fractures was demonstrated in the right upper quadrant: old fractures of the ulnar shaft with abundant callus formation were also seen. A diagnosis of osteogenesis imperfecta congenita was made. The foetus was delivered as a breech over a medio-lateral episiotomy. Special care was taken not to exert undue force in delivery. The head was delivered by Mauriceau–Smellie–Viet manœuvre under general anaesthesia. The child was a male and weighed 6 lb. 10 oz. (3,005 g.). Crepitations could be elicited in both lower legs and thighs. The skull was normal in size. The bones were thin and parchment-like. The anterior fontanelle was abnormally large. Post-natal *x*-ray examination of the infant showed multiple healed fractures of all ribs—the "string of beads" described by Potter (1952)—healed fracture of the lower aspect of the right humerus, fracture of the mid-shaft of the right radius with abundant callus, recent fracture of the right ulnar shaft, recent and old multiple fractures of both femoral shafts, and recent fractures of both tibiae and fibulae. The other bones were normal. Eight weeks after the birth of the child an *x*-ray film of the bones showed good healing with callus formation.

Adatia (1957) found one case of osteogenesis imperfecta congenita among 2,500 deliveries. His patient was a 22-year-old 3-para who presented herself for antenatal supervision at the seventh month. Her previous deliveries had been normal. A breech presentation of the foetus was recognized later, and, though repeated attempts were made, external version failed. However, spontaneous version took place before term, and she delivered at full term a live male child weighing 4 lb. 10 oz. (2,100 g.). On examination the foetus showed a skull of normal shape but with large anterior, posterior, and lateral fontanelles and wide sutures. The bones of the calvarium were found to be soft and wormian when palpated. The sclera of the eyes was white. The arms were normal. The thighs and legs were bowed, and crepitations suggestive of fractures could be elicited at their lower ends. The post-natal *x*-ray film showed multiple fractures of the foetus, involving the ribs and the extremities. The child lived for only seven months. The patient subsequently gave birth to another child, also affected by the same disease. I know of only one instance of this condition in a series of 543 abnormal babies (Sarma, 1958). A report of this case follows.

CASE REPORT

A 22-year-old 2-para was admitted to hospital at full term, having had labour pains for four hours prior to admission. Her previous obstetric history was not relevant, although she had been delivered with the aid of forceps and had developed post-partum eclampsia. Her current pregnancy had been uneventful.

On general examination she was found to have slight oedema of the feet and an elevated blood-pressure (150/100). There was no albumin in the urine. Obstetric examination showed that the uterus was full term in size. There were no abnormalities in shape. There was no polyhydramnios. The foetus was longitudinal in lie, flexed in attitude, vertex in presentation, and left occipito-anterior in position. The head was fixed. The foetal heart could be heard well in the left quadrant of the abdomen. Within an hour after admission the membranes ruptured. This

*From a dissertation for the M.D. degree of Cambridge University.

was followed soon after by the birth of a live female child weighing 4 lb. 8 oz. (2,040 g.). The third stage was normal. The placenta was healthy and weighed 12 oz. (340 g.). The head of the baby appeared to be slightly enlarged. By palpation the fontanelles were found to be somewhat large in size and slightly tense. Multiple wormian bones could be palpated over the head. Bony spicules could be felt at the periphery of the cranial bones. The child showed deformities of both its lower limbs. There was no blue discoloration of the sclera of the eyes. No other malformations, such as cleft-palate, spina bifida, or talipes-equino-varus, were observed.

FIG. 1.—Radiograph showing slight degree of hydrocephalus.

FIG. 2.—Radiograph showing evidence of healing of old fractures.

Four days after the child was born *x*-ray examination showed a slight degree of hydrocephalus (Fig. 1). It also revealed imperfect formation of the membrane bones. There were multiple fractures of the left humerus with callus formation of one side, and the tibiae showed evidence of healing of old fractures (Fig. 2).

There was little doubt that this condition was in fact osteogenesis imperfecta congenita. Indeed, had there been any occasion to radiograph this patient before birth a splendid opportunity might have been present to demonstrate this abnormality of the foetus *in utero*.

COMMENT

The great interest of this bone condition lies in the fact that it should be possible to demonstrate it on antenatal *x*-ray films. The obstetric implication, once the presence of this condition is recognized, is that great care has to be taken to avoid force and unnecessary manipulations. Even slight trauma may fracture the bones. Defective ossification of the cranial bones gives the appearance of a jigsaw puzzle owing to the fact that they are largely made up of wormian bones. On rare occasions vaginal examination may reveal the peculiar consistency of the foetal skull on palpation, enabling an intra-partum diagnosis to be made.

In most cases of the foetal type of this disease the infants are stillborn, or live only for a short time (Teall, 1934).

I am grateful to Dr. S. Abraham, professor of obstetrics and gynaecology, Madras University, and superintendent of the Government Women and Children's Hospital, Egmore, Madras, for her generous consent to my use of clinical material from the hospital. The photographs are reproduced by permission of the Government Women and Children's Hospital, Egmore.

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The cost (including debt charges) of running the London County Council day nurseries in 1959–60 was £922,267 after deducting sundry income of £49,485 (for example, payments by staff for meals, etc.). Contributions from parents in 1959–60 amounted to £157,548. Where a person making use of a day nursery expresses inability to afford the approved charge, a scale of assessment (approved by the Health Committee) is prescribed. Assessed payments are related to the income of the parents after deductions for rent and other necessary expenses—the extent of the latter varying with the number and composition of the household. While simple in operation the scale is necessarily complex in structure to allow for a multiplicity of incomes and family circumstances. Over the 12 months ending October 1, the average daily attendance in a quarter ranged between 87.9% and 90.1%, expressed as a percentage of places approved for daily use.

Reviews

PREMATURITY

Prematurity. The Diagnosis, Care, and Disorders of the Premature Infant. By Beryl Corner, M.D.(Lond.), F.R.C.P. (Lond.). Foreword by A. V. Neale, M.D.(Birmingham), F.R.C.P.(Lond.), D.P.H. (Pp. 587+xiii; illustrated. £5 5s.) London: Cassell. 1960.

This is probably the largest book yet published on prematurity. Its 587 pages are divided into five parts and there are four appendices. The first two parts are general and factual, concerned with the incidence, causes, and prevention of prematurity, diagnosis, metabolism, and nutrition, ending with a summary of the problems encountered. The third part, the care of the premature infant, largely recounts the author's long and close practice experience with the subject and is excellent. The fourth section, disorders of the premature infant, includes chapters on pathology and ophthalmology, both of great importance, and is really a "textbook of prematurity" in its own right. In the last part, on prognosis, the progress and survival of premature infants are discussed, and there is a final chapter on morbid anatomical findings. The appendices are devoted to medical and nursing procedures, antibiotics, and the composition of proprietary milk preparations.

Any adverse criticisms are of minor significance and must not detract from the value of the work as a whole. There are many typographical errors, some mis-spellings, and a maddening index differentiation between microphthalmia and microphthalmos and between hydrocephalus and hydrocephaly. There is no mention of the value of chromatography nor of the recent developments in the study of chromosome abnormalities. Recommended treatment is sometimes vague—for example, "As soon as the diagnosis is suspected 50 per cent dextrose solution should be given intravenously." The volume to be infused is surely of paramount importance.

Anyone wanting to learn the practical aspects of the care of the premature infant, or seeking references to particular aspects, will find this book invaluable. Those already experienced in this field may disagree with some of Dr. Corner's dicta, but will surely be stimulated to re-examine their own findings and practice in the light of her experience. The 136 illustrations are generally excellent and there are four coloured plates. This is indeed a magnum opus.

WILFRID GAISFORD.

HUMAN GROWTH

Human Growth. Symposia of the Society for the Study of Human Biology. Volume III. Edited by J. M. Tanner. (Pp. 120; illustrated. 30s.) Oxford, London, New York, Paris: Symposium Publications Division, Pergamon Press. 1960.

This little book is the report of a symposium organized by the Society for the Study of Human Biology. Much of what the book contains will already be familiar to those who have a special interest in this field, but even for these such papers as Roy Acheson's on the effects of nutrition and disease on human growth provide a useful review. A. W. Boyne tells us that, while mankind has been getting taller, the boys at Eton and Marlborough appear now to have achieved their maximum heights. He repeats the information, which has already reached us on the journalistic grape-vine, that Aberdeen girls at the 11+ examination are now more intelligent than the boys, who have been left behind sadly in the last 20 years. He suggests that there is an intellectual growth spurt, corresponding to the pubertal linear growth spurt, and with puberty getting earlier (four months in every decade according to Tanner's investigations) many girls are receiving this stimulus to intelligence at 11–12 years. Tanner writes thoughtfully on the genetics of human growth; characteristically, he lucidly states the limits of the known and defines the targets for to-morrow. D. F. Roberts, who has been measuring Africans, makes some interesting suggestions with regard to the effect of race and climate on growth. Only a summary of McKeown's paper on the influences affecting prenatal growth in man is published, but sufficient to encourage the reading of the promised monograph. The book is finely printed, but there is no index.

D. V. HUBBLE.

LIMB EMBOLISM

Arterial Embolism in the Limbs. The Clinical Problem and its Anatomical Basis. By A. L. Jacobs, M.A., D.M.(Oxon.), F.R.C.P. Foreword by C. G. Rob, M.C., M.A., M.Chir. (Cantab.), F.R.C.S. (Pp. 200+xii; illustrated. 35s.) Edinburgh and London: E. and S. Livingstone, Ltd. 1960.

One of the difficulties that is commonly encountered in treating the occasional rare situation is lack of sufficient personal experience to guide the conduct of the case. This makes the present monograph of particular value, since the data on embolism to the limbs are set out very clearly and the conclusions which are so helpful in clinical assessment are given great prominence. This book stands as a tribute to the value, not just of the collection of clinical data, but of its critical sifting by an experienced clinician. I think there is no statement made in this book which is not backed up by the evidence, and by a comparison with evidence from other sources. This gives a great deal of confidence when the main conclusions, which are so clearly set out, are reached. There are books in which references to other work are given which are almost put in as make-weight, but here all the evidence is weighed, and, where found wanting, rejected. Most aspects of the subject are covered and the clinician would feel more confident in handling a case of limb embolism after reading the clinical sections, and those interested in the experimental aspect of arterial obstruction would gain much from the injection studies and observations on arterial block.

It must be very rarely that in such a short compass so much useful information has been gathered together in a way which makes the points clearly and succinctly and yet gives the impression of a fine balance without dogmatism.

W. S. PEART.

OPHTHALMOLOGICAL NOTES

Lecture Notes of Ophthalmology. By Patrick D. Trevor-Roper, M.A., M.D., B.Chir (Cantab.), F.R.C.S., D.O.M.S. (Eng.). (Pp. 94+v; illustrated 12s. 6d.) Oxford: Blackwell Scientific Publications. 1960.

The modern medical curriculum is so extensive that undergraduate students can have little time or energy left over for the detailed study of the diseases of a very highly specialized organ of sense, and when, as often happens, one asks what book should be read, the reply is not easy. Provided a student has attended adequate lectures on ophthalmology his easiest method of revision is perhaps to study the illustrations and their texts in a standard work. The author of this

book has endeavoured to combine undergraduate lectures set in large type with a fair number of illustrations within the compass of 90 small pages. Such a task, inevitably involving omissions, has been accomplished, and the modern student now has an ophthalmological digest which covers his basic needs and which can be read through on a train journey of 100 or so miles. The book is well produced, the illustrations are clear and well chosen, but could with advantage be even more numerous, for in work of this scope there is much in favour of a picture book. There is little doubt that *Lecture Notes on Ophthalmology* will prove popular with students.

HAROLD RIDLEY.

NEUROSURGICAL ANAESTHESIA

A Practice of General Anaesthesia for Neurosurgery. By Robert I. W. Ballantine, M.R.C.S., L.R.C.P., D.A., F.F.A. R.C.S. With the collaboration of Ian Jackson, M.R.C.S., L.R.C.P., D.A. Foreword by J. E. A. O'Connell, M.S., F.R.C.S. (Pp. 152+viii; illustrated. 27s. 6d.) London: J. and A. Churchill, Ltd. 1960.

The purpose of this small monograph is to describe in detail the general anaesthetic methods that the authors have found simple and efficient in neurosurgery. This book emanates from St. Bartholomew's Hospital and the standard technique described is based upon endotracheal nitrous oxide, oxygen, and trichlorethylene with local infiltration of 1 in 500,000 adrenaline. It is only fair to point out that widely differing alternative techniques are preferred in other centres.

The first two chapters on general considerations and on intracranial pressure are especially lucid and valuable. There are useful sections on hypothermia and induced hypotension. It is a pity that the promising new development of lowering the intracranial pressure by infusion of 30% urea with invert sugar came too late to receive more than brief mention.

The trainee anaesthetist does not always have the opportunity of comprehensive experience in this subject and will therefore find especially useful the two detailed chapters on individual operations and also that on pre-and post-operative care.

The illustrations are in general first-class, but perhaps too much space has been devoted to the reproduction of many anaesthetic record cards: a smaller number of these could have sufficed. The book is well produced, apart from a few minor errors in proof-reading. Most anaesthetists will consider it a worth-while addition to their bookshelves.

C. F. SCURR.

DIGEST OF SOCIAL MEDICINE

A Synopsis of Public Health and Social Medicine. By A. J. Essex-Cater, M.R.C.S., L.R.C.P., D.C.H., D.P.H., D.I.H., F.R.A.I. Foreword by J. M. Mackintosh, M.A., M.D., LL.D., F.R.C.P. (Pp. 563+xii; illustrated. 55s.) Bristol: John Wright and Sons, Ltd. 1960.

As a general rule, synoptic textbooks are difficult to read, and therefore not conducive to easy learning. In this volume the author has made an effort to overcome this by introducing some brief discussion on controversial issues and even expressing his own views fairly definitely. He has thus succeeded in a considerable measure in enlivening and giving interest to what could otherwise tend to be a potted version of legislation and government reports. The synopsis must always presuppose some basic knowledge of the subject and is not intended to be a primer for the novice. Its main function, and this volume should prove most satisfactory, is to provide a quick source of reference, a means of quick revision, and for amplifying knowledge already acquired.

One problem which the author has had to face has been what to leave out, and he has obviously come down on the side of completeness. Even the brief accounts of elementary statistical methods should prove useful. The opening chapter on the health services and the later one on the welfare services are excellent and could well serve as a reference manual for every registered medical practitioner. The chapters on epidemiology, communicable diseases, and occupational health deal adequately with these aspects of preventive medicine.

Dr. Essex-Cater is to be congratulated on the care and thoroughness which has gone into the preparation of this book. It will obviously have a special appeal for those working in Public Health and Social Medicine, but it deserves a much wider public. It provides a most valuable source of reference for any doctor.

ANDREW B. SEMPLE.

URINARY LITHIASIS

Treatment of Urinary Lithiasis. Compiled and edited by Arthur J. Butt, B.S., M.D., F.A.C.S. (Pp. 577+xxii; illustrated. £8 8s. 6d.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

Following an earlier volume on the *Etiologic Factors in Renal Lithiasis* Dr. Butt has sought the co-operation of 32 authors, many of whose names are well known in American urology, to produce the present volume on the treatment of urinary lithiasis. The amount of space which has been allocated for the consideration of different aspects of the subject does not always reflect their importance in practice, so that some questions, the answers to which the reader may search for, are not always there.

Dr. Butt has been responsible for the first rather long but excellent account of the history of the treatment of urinary lithiasis. This is followed by the consideration of the surgery of renal stone, including the anatomical approach in operations for calculous disease of the urinary tract, pre- and post-operative care (a very long article), anaesthesia, and surgical management. The section on surgical management gives too little of a detailed character and leaves important gaps such as the assessment of the place of partial nephrectomy in the treatment of renal stone, a popular operation in Great Britain. Surgical treatment of stone in the ureter is well covered from both an instrumental and an operative point of view. The medical management of stone and certain special groups of stones, such as recumbency calculi and those which form as a result of hyperparathyroidism, receive mention. Other chapters deal with the use of aluminium gels for the prevention of phosphatic stone, cystine lithiasis, and special measures for the treatment of uric acid stones and oxalate stones. Approximately one-third of the book deals with stones in the bladder, urethra, and prostate. Instrumental and operative removal of vesical calculi is adequately discussed, and there are interesting sections on the treatment of urethral and prostatic calculi.

The book is useful for the general surgeon perhaps rather more than the urologist, and contains much that is helpful. It is well illustrated and the author and subject indices are carefully prepared.

L. N. PYRAH.

GASTRIC CYTOLOGY

Gastric Cytology: Principles, Methods, and Results. By Rudolph Otto Karl Schade, M.D.(Dunelm), M.D.(Tübingen), L.R.C.P., M.R.C.S. (Pp. 83+viii; illustrated. 35s.) London: Edward Arnold (Publishers) Ltd. 1960.

In this monograph the author has given a comprehensive account of the methods used and the results obtained by him in the examination of stomach washings for malignant cells in cases of possible gastric carcinoma. He does not favour the use of gastric brush (Ayre and Oren) or of the abrasive balloon (Panico and others) which have been recently introduced, but prefers the simple lavage technique with saline solution as employed at the Vincent Memorial Hospital. The preparation of the specimens for cytological examination, stained by Papanicolaou's technique, is given in detail. The many and various types of cells found in gastric washings and derived from the alimentary and respiratory tracts are described and illustrated, as also the malignant cells seen in carcinoma of the stomach. Most of the illustrations are good.

The results obtained by Schade using a simple lavage technique are impressive. Since 1954 up to the time of publication, 2,443 patients were investigated and 3,280 cytological examinations performed. In 252 cases subsequently proved to be malignant 97.6% were cytologically positive; in 251 non-malignant conditions such as peptic ulcer 94.8% were cytologically negative. There were six false negatives in the first group and 13 false positives in the second. The majority of cytologists working in this field have been less successful. It is significant that 10.5% of the cancer cases were undiagnosed by radiology, and among these were 16 cases of surface carcinoma unsuspected clinically. The detection of carcinoma at this early stage, when the prognosis following operation is so much better, is obviously an important advance in diagnosis. This book provides much information for all those interested in the subject.

J. BAMFORTH.

CARDIAC AUSCULTATION

Cardiac Auscultation including Audio-visual Principles. By J. Scott Butterworth, M.D., Maurice R. Chassin, M.D., Robert McGrath, M.D., and Edmund H. Reppert, M.D. Second edition (revised and enlarged). (Pp. 102; illustrated. $6.25.) New York and London: Grune and Stratton. 1960.

In this up-to-date dissertation the authors have as their theme the combination of the auditory and the visual record. This can be done on a fluorescent screen. The general foundations of the art are well set out. The scientific basis is well explained. There is some historical background. The word "stethogram" is used to mean the record of the heart sounds, "phonocardiogram" is held to include an electrocardiogram. The student might wonder why the two heart sounds are so different: he is not told. The comparison of the pulmonary and aortic second sounds is deprecated: one must recognize and assess the aortic and pulmonary components. The position of the patient is hardly considered enough. Gallop rhythm is not always fast. The name of Potain might come in here, and also that of Skoda for "split" sounds. Gibson's wonderful account of the murmur of the patent ductus (its plural is not ducti) should not be omitted. "Machinery" is still the epithet, but what machine makes a noise like that? The records are excellent. The print is clear and the type well chosen. There is much useful information that the student should be able to assimilate, so long as he does not place too much reliance on his ears and forget the other senses, despite the authors' stress on the visual record. They should remember the Song of the Stethoscope by their countryman, Oliver Wendell Holmes.

TERENCE EAST.

CHEMICAL CONCEPTS OF PSYCHOSIS

Chemical Concepts of Psychosis. Proceedings of the Symposium on Chemical Concepts of Psychosis held at the Second International Congress of Psychiatry in Zurich, Switzerland, September 1-7, 1957. Edited by Max Rinkel and Herman C. B. Denber. (Pp. 485+xxi; illustrated. 63s.) London: Peter Owen, Ltd. 1960.

When this reviewer entered psychiatry from medicine twenty-five years ago it was thought a sign of somewhat disturbed judgment to believe that this specialty was bound to return again to general medicine in spirit as well as in deed as the treatments of psychiatric illnesses were found to be increasingly similar to those of other illnesses, especially in their response to physical and biochemical treatments. Admittedly, at that time, apart from the malarial treatment of G.P.I., there were few physical treatments of mental illness except some sedative drugs.

This book, however, is yet another indication of the tremendous progress and revolution in thought that has happened since then. It records the proceedings of a special symposium held at the Second International Congress of Psychiatry in Switzerland, in September, 1957. It contains discussions by eminent workers from many countries on the theoretical background and the biochemical approaches that have led on to the large amount of work now being undertaken into the causes of such illnesses as depression and schizophrenia, and in the development of more practical physical treatments to help them.

The editors are certainly to be congratulated on collecting in this volume so much useful information helpful to progress in this rapidly developing field. It is, however, a book largely for the specialist, and is also a valuable reference book; most of it would still be hard and difficult going for the general practitioner. In fact, the language of the psycho-analyst is now child's play compared to that of the high-powered biochemist discussing the mind of man.

WILLIAM SARGANT.

SMALL-BOWEL DISORDERS

Radiologic Examination of the Small Intestine. By Ross Golden, M.D. Second edition. (Pp. 560+xxv; illustrated. £11 8s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1959.

The first edition of this book was published in 1945, and since then there have been many developments in the radiological study of small-bowel disorders. In this second edition Dr. Golden has presented the results of 30 years' intensive radiological experience of the investigation of small-bowel disorders and an extensive digest of the relevant literature in a masterly way.

In a general introduction the methods of investigations which are applicable are discussed, including the use of the inflatable double-lumen Miller–Abbott tube in obstruction or bleeding of unknown cause. The embryology, anatomy and physiology, and normal radiological appearances of the small bowel are clearly described. A wide variety of developmental conditions, including intra-thoracic duplications of the jejunum and invagination of Meckel's diverticulum, are

illustrated. The effect of drugs and of food on small-intestine contractions and mucosal pattern is discussed, and allergic and functional disorders are considered.

The chapters on gas distension of the small intestine and ileus and the use of the Miller–Abbott tube in diagnosis and treatment deserve careful reading by all concerned in the diagnosis and treatment of cases of intestinal obstruction. It is interesting to learn that the correct insertion of the tube was the responsibility of one nurse-technician in a large hospital. Success in intubation occurred spontaneously in only 87 of 300 patients in a two-year period; correct placement of the tube tip under fluoroscopic control resulted in success in another 113 more. Clearly, active radiological assistance is advisable if the method is to be applied effectively.

The inflammatory diseases, Crohn's disease, tuberculosis, and an interesting group of non-sclerosing enteritis cases affecting the terminal ileum are well discussed. The chapter on neoplasms is based on a personal series of 74 cases, and the discussion of difficulties and errors of diagnosis is most helpful. A valuable chapter on parasitic infestation is contributed.

This book will remain, for many years, a standard work of reference and of stimulus to those actively engaged in the study of pathology in this important and still somewhat neglected region of the alimentary tract. The illustrations and general presentation of the book are first class.

F. PYGOTT.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

The Practice of Medicine. Edited by Sir John Richardson, M.V.O., M.A., M.D.(Cantab.), F.R.C.P. 2nd edition. (Pp. 973 + viii; illustrated. 37s. 6d.) London: J. and A. Churchill Ltd. 1960.

Valvular Disease of the Heart in Old Age. By P. D. Bedford, M.D., M.R.C.P., and F. I. Caird, D.M., M.R.C.P. (Pp. 194 + x; illustrated. 30s.) London: J. and A. Churchill, Ltd. 1960.

Recent Advances in Pathology. Edited by C. V. Harrison, M.D. Seventh edition. (Pp. 459 + xi; illustrated. 48s.) London: J. and A. Churchill, Ltd. 1960.

Les Entretiens de Bichat. 1960. Chirurgie-Spécialités. Published under the direction of R. Gueulette, J. Hepp, Y.-J. Longuet, and M. Roux. (Pp. 557. No price.) Paris: L'Expansion Scientifique Française. 1960.

Les Entretiens de Bichat. 1960. Médecine. Published under the direction of Guy Laroche and L. Justin-Besançon. (Pp. 582. No price.) Paris: L'Expansion Scientifique Française. 1960.

Les Entretiens de Bichat. 1960. Thérapeutique. Published under the direction of Guy Laroche and L. Justin-Besançon. (Pp. 172. No price.) Paris: L'Expansion Scientifique Française. 1960.

Modern Trends in Cardiac Surgery. Edited by H. R. S. Harley, M.S., F.R.C.S. (Pp. 282 + xiii + 12; illustrated. 70s.) London, Toronto, Sydney, Wellington, Durban: Butterworths. 1960.

Studii si Cercetari de Medicina Interna. Institutul de Medicina Interna, Romine. (Pp. 108. No price.) Bucharest: Academiei Republicii Populare Romine. 1960.

Studii si Cercetari de Inframicrobiologie. Institutul de Inframicrobiologie, Romine. (Pp. 137. Lei 6.) Bucharest: Academiei Republicii Populare Romine. 1960.

Sclerozele Pulmonare. By Acad. N. Gh. Lupu, C. Velican, C. Racoveanu, and M. Gociu. (Pp. 373; illustrated. Lei 29.90.) Bucharest: Academiei Republicii Populare Romine. 1960.

Recent Advances in Biochemistry. By T. W. Goodwin, D.Sc., F.R.I.C. 4th edition. (Pp. 301 + vi; illustrated. 50s.) London: J. and A. Churchill Ltd. 1960.

Disease in Infancy and Childhood. By Richard W. B. Ellis, C.B.E., M.A., M.D., F.R.C.P. Third edition. (Pp. 714 + vii; illustrated. 55s.) Edinburgh and London: E. and S. Livingstone, Ltd. 1960.

Cell and Tissue Culture. By John Paul, M.B., Ch.B., Ph.D., M.R.C.P.Ed. Second edition. (Pp. 312 + xi; illustrated. 32s. 6d.) Edinburgh and London: E. and S. Livingstone, Ltd. 1960.

Antenatal and Postnatal Care. By F. J. Browne, M.D. (Aberd.), D.Sc., F.R.C.S.(Edin.), F.R.C.O.G., and J. C. McClure Browne, B.Sc., M.B., B.S., F.R.C.S.(Edin.), F.R.C.O.G. Ninth edition. (Pp. 435 + viii; illustrated. 45s.) London: J. and A. Churchill Ltd. 1960.

Adventure to Motherhood. The Picture-story of Pregnancy and Childbirth. By J. Allan Offen, M.D. (Illustrated. $2.95.) Miami: Audio Visual Education Company of America, Inc. 1960.

Erläuterndes Anatomisches Wörterbuch. Vergleichende Uebersicht der Baseler, Jenaer und Pariser Nomenklaturen, Gruppiert nach Organen. By Tibor Donath. (Pp. 538. £2 10s.) Budapest: Terra Budapest Verlag Medicine. 1960.

Mary Queen of Scots. The Daughter of Debate. Sir Arthur Salusbury MacNalty, K.C.B., M.A., M.D.(Oxon.), F.R.C.P., F.R.C.S. (Pp. 247. 21s.) London: Christopher Johnson Publishers Ltd. 1960.

A Mission Doctor Sees the Wind of Change. By E. W. Doell. (Pp. 211. 18s.) London: Christopher Johnson. 1960.

Problems in Photosynthesis. By W. Bladergroen, Ph.D. (Pp. 198 + xiii; illustrated. 84s.) Springfield, Illinois: Charles C. Thomas. 1960.

Selected Papers from the Institute of Cancer Research: Royal Cancer Hospital and from the Royal Marsden Hospital 1958. Vol. 13. (Pp. 1,016 + xxi; illustrated. No price.) Published by order of the Committee of Management of the Institute and the Board of Governors of the Royal Marsden Hospital, London. 1960.

Medical and Dental Aspects of Fluoridation. By W. A. Cannell, M.R.C.S., L.R.C.P., D.P.H., L.D.S. R.C.S. (Pp. 125 + vii. 15s.) London: H. K. Lewis and Co. Ltd. 1960.

Varicose Veins. A Practical Manual. By R. Rowden Foote. With the assistance of A. Gordon Dingley, M.A., M.Chir. (Cantab.), F.R.C.S. Third edition. (Pp. 355 + xx; illustrated. 63s.) Bristol: John Wright and Sons, Ltd. 1960.

Transactions of the International Society of Plastic Surgeons. Second Congress, London 1959. Edited by A. B. Wallace, M.Sc., F.R.C.S.Ed. (Pp. 589 + xxiv; illustrated. 90s.) Edinburgh and London: E. and S. Livingstone. 1960.

Occupational Diseases and Industrial Medicine. By Rutherford T. Johnstone, M.D., and Seward E. Miller, M.D. (Pp. 482 + vii; 84s.) Philadelphia and London: W. B. Saunders Company. 1960.

Modern Trends in Urology. (Second Series.) Edited by Sir Eric Riches, M.C., M.S., F.R.C.S. With a Foreword by A. Clifford Morson, O.B.E., F.R.C.S. (Pp. 257 + xvi + 13; illustrated. 70s.) London: Butterworths. 1960.

The Head, Neck, and Trunk. Muscles and Motor Points. By Daniel P. Quiring, Ph.D. Second edition revised and edited by John H. Warfel, Ph.D. (Pp. 124; illustrated. 24s. 6d.) London: Henry Kimpton. 1960.

A Primer of Electrocardiography. By George E. Burch, M.D., F.A.C.P., and Travis Winsor, M.D., F.A.C.P. Fourth edition. (Pp. 293; illustrated. 37s. 6d.) London: Henry Kimpton. 1960.

The Anonymous Mycobacteria in Human Disease. The Sixth Annual Ivan H. Mattson I Memorial Conference, of the University of Texas Southwestern Medical School and Dallas Tuberculosis Association. Edited by John S. Chapman, M.D. (Pp. 173 + x; illustrated. 60s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications Ltd. 1960.

Radiation Injury in Man. Its Chemical and Biological Basis, Pathogenesis and Therapy. By Eugene P. Cronkite, M.D., and Victor P. Bond, M.D., Ph.D. (Pp. 200 + vii. 52s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications Ltd. 1960.

Chemical Osteosynthesis in Orthopaedic Surgery. By Michael P. Mandarino, M.D. (Pp. 72 + x; illustrated. 36s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications Ltd. 1960.

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THE WIND OF CHANGE

The person carrying out artificial respiration is usually a layman, and, by medical standards, has only elementary understanding of the anatomical and physiological problems. Consequently one method must be chosen as standard or routine, and taught widely, in the hope that in most cases it would be the method best suited to the operator's skill and to the environmental circumstances. At present the Holger Nielsen method is the favoured one. It lends itself to lay instruction as a mechanically fairly precise manœuvre, and it is capable of endless repetition on volunteers as training subjects. But in the last year or two powerful advocacy has appeared for the adoption of what has become known as the expired-air method of artificial respiration. In this, the expired air of the operator is blown into the lungs of the moribund subject. There is little need to refer to recent literature to discover its effectiveness; for a long time it was more generally known as mouth-to-mouth artificial respiration. The description in the Bible of what we might now call "Elisha's method"[1] is a classical one, and from Vesalius to the present day numerous writers[2 3] have testified to the success of it. Moreover, it is of interest that the several recent physiological studies of the method—for example, that by Cox and colleagues[4]—indicate that the tidal volumes, and levels of carbon dioxide and oxygen in the subject's blood as well as the operator's, are all satisfactorily maintained. There can therefore be little dispute that expired-air or mouth-to-mouth artificial respiration by Elisha's method is as effective in the subject made moribund by accident as is intermittent positive pressure respiration in the patient deliberately made apnoeic during anaesthesia. It is also becoming clear that the tidal volumes resulting from the manual compression of the chest are not only smaller than from intermittent positive pressure respiration[5] but are adequate only in the hands of experienced operators and in healthy patients with elastic chest walls; in others, manual methods may be quite ineffective. The problem is now whether the expired-air method should be introduced into everyday use and the chest-compression method abandoned. The main objections have been put concisely by one group[6] as being "(1) a reluctance and apprehension to breathe into an apnoeic person, the operator fearing infection and contamination; (2) invariable hyperventilation and frequent experiences of dizziness and fatigue resulting in decreased efficiency; (3) reluctance to participate in training programmes which teach this method: and (4) a risk of over-distension of the lungs, especially in infants and children." Another recent report[7]—on 21 Swedish cases—emphasizes that convulsions, trismus, and vomiting often accompany acute asphyxia. A minority (six) of the rescuers in that series are recorded as having felt distressed over their experience, but only in retrospect after completing the task.

Most of these objections are overcome by using a simple inflating bellows, of which several have been designed.[8 9] If they are to be used, they must be kept very readily available. This is easily done in a clinical environment; some hospitals keep one of them in every ward. The same might be done at first-aid posts and dressing-stations in factories and mines. The reluctance to make personal contact with the subject is an understandable one. The following description was written in 1796[2]: "But as the insufflation of Air by mouth is a very Toilsome and Loathsome Act, and since accordingly an otherwise laudable delicacy of feeling usually prohibits both the Physician and other People of Propriety from using this method, especially in adults or People of advanced years who have been drowned, it is of only little use." To some extent this difficulty is overcome by the use of such devices as the Safar airway,[10] the Brook airway,[11] and the Seeler mask.[12] The simplest of all these perhaps is an ordinary anaesthetic mask,[13] the operator blowing through the hole while holding the mask firmly on the subject's face. A real difficulty in connexion with the widespread substitution of the expired-air method for the Holger Nielsen is the provision of subjects on whom large numbers of laymen can practise and learn the technique. To overcome it manikins have been designed[14–16] on which the whole procedure can be performed with lifelike realism. This no doubt would go a long way to provide reasonable training.

The question, Will more lives be saved by Elisha's method than by the Holger Nielsen? is

[1] Kings 2, chapter IV, verse 34.
[2] Herholdt, J. D., and Rafn, C. G., *Life-saving Measures*, 1796, Copenhagen.
[3] Waters, R. M., *J. Amer. med. Ass.*, 1943, **123**, 559.
[4] Cox, J., *et al.*, *Lancet*, 1960, **1**, 727.
[5] Macintosh, R. R., and Mushin, W. W., *Brit. med. J.*, 1946, **1**, 908.
[6] Tomashefski, J. F., and Oliver, T. K., *J. Amer. med. Ass.*, 1960, **172**, 1888.
[7] Elam, J. O., Ruben, A. M., and Greene, D. G., ibid., 1960, **174**, 13.
[8] Macintosh, R. R., *Brit. med. J.*, 1953, **2**, 202.
[9] Hillard, E. K., and Mushin, W. W., ibid., 1960, **2**, 729.
[10] Safar, P., and McMahon, M., *J. Amer. med. Ass.*, 1958, **168**, 1459.
[11] Dobkin, A. B., *Lancet*, 1959, **2**, 662.
[12] Seeler, H. W., *U.S. Armed Forces med. J.*, 1959, **10**, 761.
[13] Mushin, W. W., *Med. ill. (Lond.)*, 1949, **3**, 495.
[14] Ruben, H., *Brit. med. J.*, 1960, **2**, 463.
[15] Dobkin, A. B., *Lancet*, 1959, **2**, 662.
[16] *Brit. med. J.*, 1960, **2**, 1819.
[17] Matthews, O., *Lancet*, 1960, **1**, 1070.

crucial, and its answer can come only from carefully collected observations made from the field of first aid rather than from the laboratory. We are still uncertain whether the new method will bring a greater liability to such hazards as the inhalation of vomit, over-distension and damage to the lungs by the high positive pressures which a vigorous operator can produce, the difficulty of maintaining a clear airway, the occurrence of cross-infection, the difficulty for the operator in maintaining ventilation for long periods of time; this will be learnt only by careful and patient observation in a busy first-aid area. There is already evidence, for example, that the method can empty the stomach of its contents.[17]

Certain things seem clear already. Every medical student must be taught, and indeed every doctor should know, that intermittent positive pressure is the most effective way of ventilating an apnoeic patient, and that this can be done in as simple a manner as holding a face-mask on the face and blowing into the hole. A simple inflating bellows of the type already mentioned would be a valuable if not an essential object in every ward, casualty room, and other places where artificial respiration might be performed by a doctor or nurse. The Elisha or expired-air method is worthy of the closest interest and trial. It ought to be adopted, at the very least, on an experimental basis by selected first-aid units which have frequent calls made on them for artificial respiration. Their results, and the observations of both medical teachers and lay first-aiders, could then be compared with those from other first-aid units using the more classical methods. In this way an objective comparison might be made of the real effectiveness in actual first-aid practice of the life-saving powers of one method as against another. If indeed the superiority of the expired-air method is certain under field conditions, the liability to undesirable complications is not introduced, and the problem of teaching the method is solved, there will then be little difficulty in overcoming the natural and understandable reluctance of leaders in the first-aid world to giving up such a well-tried, clearly understood, and easily taught method as the Holger Nielsen.

EPIDEMIC BRONCHIOLITIS

In Great Britain epidemic bronchiolitis in infants is commonest in winter and early spring. Few big centres of population escape in any one year.[1] Most writers on the subject[2–5] agree that it seems to spread to infants from older members of the family who are suffering from a mild upper respiratory infection. The negative bacteriological findings, combined with lack of response to antibiotics, and its spread from contacts with apparent mild virus infection, suggest that the cause is due to a virus or group of viruses at present unknown.[2–6]

While it may appear under many different names, such as asthmatic bronchitis, capillary bronchitis, virus pneumonia, and epidemic bronchopneumonia, the term epidemic bronchiolitis would seem to be the most satisfactory from both a pathological and clinical point of view. In fact, as J. B. Heycock and T. C. Noble have pointed out, this condition (with the exception of staphylococcal pneumonia) is synonymous with bronchopneumonia in infants.

Though it does occur in children of any age, the disease appears to produce serious effects only in children under the age of 2 years, and especially in those under 6 months. Even in this younger age group the symptoms can vary from the mildest upper respiratory infection to the most severe form of pneumonia seen—progress from the one to the other frequently taking only a few hours. It has been estimated that only 18% need admission to hospital.[1] Modern treatment has reduced the mortality to 1–5%,[3–7] but the wide distribution of the disease among the population of young babies means that several of them die every year of it. While there is nothing to distinguish the early stage of the condition from that of any other upper respiratory infection, the onset of a severe paroxysmal cough very like whooping-cough, combined with marked respiratory distress, rapid grunting respiration, and a tachypnoea with rates up to 100, associated with little or no fever, are fairly characteristic of the condition. Examination of the chest in the early stages may reveal either localized or generalized crepitations. Some patients, especially those under 6 months, present the picture of bronchiolar obstruction, with general emphysema and fine rhonchi, so characteristic of asthma. But asthma is rare in children of this age and normally tends to clear rapidly in twenty-four hours. In an epidemic the distinction is usually easy.

Radiography of the chest may show various appearances, the two most common being normality and gross emphysema. Sometimes it will show patches of segmental or lobar collapse and patches of pneumonia, or a combination of any of these with emphysema.

[1] *J. Coll. gen. Pract.*, 1958, No. 19, 169.
[2] Hubble, D., and Osborn, G. R., *Brit. med. J.*, 1941, 1, 107.
[3] Garrow, D. H., and Fawcett, J. W., *Lancet*, 1953, 2, 795.
[4] Morrison, B., *et al.*, ibid., 1957, 2, 1077.
[5] Disney, M. E., Sandiford, B. R., Cragg, J., and Wolff, J., *Brit. med. J.*, 1960, 1, 1407.
[6] Ross, E., *et al.*, *Postgrad. Med.*, 1957, 22, 87.
[7] Heycock, J. B., and Noble, T. C., *Brit. med. J.*, 1956, 1, 438.
[8] Dugdale, A. E., and McGeorge, M., *N.Z. med. J.*, 1960, 59, 227.
[9] Morrison, B., *Lancet*, 1955, 2, 737.
[10] High, R. H., *Pediat. Clin. N. Amer.*, 1957, 4, 183.
[11] *Text Book of Pediatrics*, 1959, edited by W. E. Nelson, Philadelphia.
[12] McLean, K. H., *Aust. Ann. Med.*, 1956, 5, 254.
[13] Fearon, B., and Bain, H., *Trans. Amer. broncho-esoph. Ass.*, 1956, 37th meeting, 33.
[14] Jackson Rees, G., *Arch. Dis. Childh.*, 1959, 34, 358.
[15] Walker, S. H., *J. Pediat.*, 1952, 41, 528.

Mortality is highest in babies under 6 months, in whom the danger signals are collapse, convulsions, and hyperpyrexia.[5 8] B. Morrison[9] was the first to show that oxygen in high concentration (80%) benefits these infants, and that restlessness is a more reliable sign of anoxia than cyanosis. She postulated that death was probably due to anoxia from mechanical obstruction of the bronchioles. This concept is confirmed by the pathological evidence.[2 5 8] R. H. High[10] and many others have stressed the dangers of dehydration due to anorexia, difficulty with feeds, hyperpnoea, and the necessity for adequate hydration, recently borne out by M. E. Disney and his colleagues.[5] Both High and Morrison report a mortality of under 1%. Antibiotics do not seem to play much part in the treatment of this condition and may be harmful in some cases, especially if broad-spectrum antibiotics are given, owing to production of gastro-intestinal symptoms and secondary dehydration. Their use would seem to be indicated in cases of difficult diagnosis, when staphylococcal pneumonia is a possibility, when the baby is moribund, and as a cover when cortisone is to be used.[5 8] Most authors[3 6 7 10 11] agree that antispasmodics, proteolytic enzymes, and aerosols containing agents for lowering surface-tension are useless and possibly harmful, but that a high humidity with plain water in the form of a fine aerosol mist is efficacious.

Pathological evidence[2 5 8 12] suggests that the obstruction in the bronchioles is due to a combination of swelling and infiltration of the bronchiolar wall, as well as to mucus probably inhaled from the larger bronchi, where it is produced in excessive quantities. Of 727 cases admitted to the Hospital for Sick Children, Toronto, between 1952 and 1955, bronchoscopic aspiration was performed on 33 severe cases without fatality by B. Fearon and H. Bain,[13] who considered that it played a prominent part in the recovery of their patients. Jackson Rees[14] reported to the British Paediatric Association in 1959 how he used bronchoscopic aspiration with relaxants and positive-pressure respiration through an indwelling tracheal catheter; of eleven moribund babies, five recovered.

Though corticosteroids have been declared ineffective,[11] their use in possibly diminishing the inflammatory reactions in the bronchioles would seem worth an extended trial. S. H. Walker,[15] comparing two groups, each containing nine severe cases, one group acting as a control, found that the administration of A.C.T.H., 20 mg. eight-hourly, relieved the bronchial obstruction in half the cases treated in less than twenty-four hours, as compared with the controls, who took five days to reach the same stage. A. E. Dugdale and M. McGeorge[6] have recently reported on the use of hydrocortisone hemisuccinate, but the effect of it is difficult to assess.

If we are to lower the mortality from this disease still further, certain measures would seem to be desirable. The outbreak of an epidemic in any town or district should be notified to general practitioners in the area and to paediatric units, so that everyone can prepare in advance to recognize and treat cases early. Correction of the anoxia and the dehydration, if necessary by intravenous fluids, are the two most important measures to institute straight away. Controlled trials on the effect of cortisone, especially in the younger infants, would be helpful. Finally, it is worth remembering than an anaesthetist colleague can be a great help in considering whether bronchoscopy or other measures should be tried, especially for those babies who have collapsed or failed to respond quickly to treatment.

SELF-MEDICATION

Though volumes have been written on the prescribing of medicine in the Health Service, much less is known about the nature and extent of self-medication. Yet vast quantities of homely remedies are bought every day, and the advertising of them is almost as elaborate an industry as the manufacture of them. Reports of harmful results sometimes point to the need for restricting the sales of certain types of drug, notably those acting on the central nervous system,[1 2] but in general the drug industry, the newspapers, and television work harmoniously with advisers from the medical profession to prevent abuses such as were common fifty years ago.

Recently an investigation by J. H. F. Brotherston and his colleagues[3] has yielded some interesting data on self-medication in an admittedly somewhat restricted sample of people. In 1954–5 the investigators carried out a survey in a London County Council housing estate built in Hertfordshire since the war. The inhabitants were thus a new community, mainly working class (skilled manual, routine clerical, shop assistant), and included a much higher proportion of young married couples with children than the general population. The inquiries were carried out by personal interview. The time of year is not stated, but presumably the inquiries extended over a number of months.

Outstanding among the medicaments taken are aspirin and laxatives. In fact aspirin is regarded as something approaching a panacea, being taken for "nerves," anaemia, coughs and colds, dental troubles,

[1] *Drug Addiction, Interim Report of the Interdepartmental Committee*, 1960. H.M.S.O.
[2] See *Brit. med. J.*, 1960, **1**, 260.
[3] Jefferys, M., Brotherston, J. H. F., and Cartwright, A., *Brit. J. prev. soc. Med.*, 1960, **14**, 64.
[4] Reid, J. J. A., *Brit. med. J.*, 1956, **2**, 25.
[5] Ibid., 1958, **1**, 572.
[6] Ibid., 1959, **1**, 776.
[7] *Annual Report, 1959–60*, Proprietary Association of Great Britain, London.

menstrual disorders, arthritis and rheumatism, headaches, sleeplessness, and backache. Laxatives, too, are popular household remedies, and in suffering regular purgation modern man is simply acting in a centuries-old tradition that has survived rational disproof. But as frequent recourse to them is known to upset normal bowel function, thus encouraging further self-medication, it is particularly dismaying to see that regular dosing of children by the calendar is still prevalent. After studying the reasons why children were dosed in this way the authors found that most of the laxatives were given "for prophylactic purposes and not in order to cure actual constipation or upsets of the digestive system." In fact 90% of the children who received them, and 44% of the adults, took laxatives for "preventive" purposes and not to remedy existing constipation. This bears out the experience of J. J. A. Reid,[4] who graphically epitomized the unfortunate end-result of abusing the child's bowel with laxatives: "That familiar sight of the hospital wards—the patient whose life is centred around the problem of when his bowels can next be blasted into reluctant activity." Tonics, throat tablets, remedies for indigestion, eye lotions, and embrocations are also among the medicines that found favour, and with them may be included vitamin tablets. However, it seems that self-medication was not in general an alternative to visiting the doctor. In fact, the data suggested it was complementary to it, for the adults who took self-prescribed medicines during the investigation "had rather higher annual G.P. consultation rates than those with a similar number of illnesses who took no self-prescribed medicines."

Many millions of pounds a year are spent on advertising household remedies in the press and on television. In response to public opinion and to the guidance of medical advisers those who publish these advertisements see that they conform to one of several codes, which are considerably more stringent than is required by law.[5,6] The code of standards of the Proprietary Association of Great Britain has recently been strengthened by the addition of the clause[7]: "No new drug or preparation can be approved for self-medication unless it can be adequately shown to the satisfaction of the Association and its medical and scientific advisers that it is safe and suitable for that purpose." Consequently harmful misrepresentation is rare and does not exemplify the general course of drug advertising. What does perhaps need some thought is whether the continued pressure to expand the market for household remedies will help "to engender the belief that good health is synonymous with the ingestion of pharmacological preparations."[4]

APPENDICULAR CALCULI

Most surgeons would agree that true stones in the appendix are something of a rarity. But perhaps it is not widely known that the commonly encountered appendicular faecalith often contains sufficient calcium in its outer part to make it radio-opaque. Thus R. Steinert and colleagues[1] found calcified faecaliths on routine radiological examination in 10 out of 104 cases of acute appendicitis, while B. Felson[2] found radio-opaque "calculi" in 25 out of 75 acutely inflamed appendices radiographed after removal. He estimated that in 9 of these the shadow was of sufficient density to have been visible if a pre-operative radiograph had been taken.

It is important that radiologists and surgeons should be aware of the relatively common occurrence of these radiological calculi, yet recent papers[3,4] have suggested that the radiographic appearances may sometimes be misinterpreted. This may lead to disastrous delay, for in 90% of the reported cases the patient is actually having an attack of acute appendicitis when the radio-opacity is first noted. Furthermore, a radio-opaque faecalith is usually a large faecalith, and it is therefore not surprising that when acute appendicitis supervenes in such circumstances the attack is likely to be a severe one, with early gangrene and perforation. Thus in B. M. Brady and D. S. Carroll's series these complications were present in no fewer than 32 out of 34 cases.[5]

The radiological features of appendicular calculi are usually sufficiently characteristic for the correct diagnosis to be suggested with some confidence. Though usually single, multiple opacities may be seen, and they will then lie in a straight or curved line, unlike the grouped arrangement of calcified mesenteric nodes. The usual diameter is 1–3 cm., the outline fairly smooth, and the shape round or ovoid. Multiple calculi may be faceted. The most characteristic single feature, other than their position, is lamination, often with relative translucency of the centre. A calculus in the right ureter provides the most likely source of confusion, not only radiologically but sometimes clinically as well. A further radiograph after the passage of a ureteric catheter may be necessary. Appendicular radio-opacities have also been misdiagnosed as gall-stones, renal stones, calcified mesenteric nodes, and phleboliths.

The clinical features are commonly those of obstructive appendicitis and its complications. The presence of a large faecalith or stone in an appendix is likely to be followed before long by the onset of inflammation, so that it is not surprising that appendicular calculi are rarely encountered as an incidental finding either radiologically or at operation. If one is discovered during radiological examination for another condition, all authors are agreed that early appendicectomy should be strongly advised.

The increasing use of straight radiography in acute abdominal emergencies will lead to the more frequent disclosure of opacities in the appendix. If mistakes are to be avoided, it is essential that radiologists and surgeons should be familiar with this condition, which is neither as uncommon nor unimportant as is sometimes assumed.

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[1] Steinert, R., Hareide, I., and Christiansen, T., *Acta Radiol. (Stockh.)*, 1943, **24**, 13.
[2] Felson, B., *Surgery*, 1949, **25**, 734.
[3] Butler, M. F., *Brit. J. Surg.*, 1959, **47**, 279.
[4] Meyerowitz, B. R., *Brit. J. Radiol.*, 1960, **33**, 631.
[5] Brady, B. M., and Carroll, D. S., *Radiology*, 1957, **68**, 648.

THE MINISTER AND THE DRUG FIRMS

The recent rumours in the press that the Minister of Health was taking a much tougher line with the pharmaceutical industry than his predecessors when negotiating renewal of the voluntary scheme for the regulation of drug prices seem to have been exaggerated. The modifications which he announced in Parliament last week, though important, are not likely to reduce the drug bill substantially.

The arrangements which have been in force since 1957 were made after the Cohen Committee had recommended that proprietary drugs in certain categories should be prescribable under the N.H.S. only if satisfactory price arrangements were made between the health departments and the manufacturers. The voluntary agreement between the Minister and the industry allowed for an initial three-year period of freedom from control of the price of a new drug. After that the price of a drug was to be fixed by reference to export prices if exports of it were substantial; otherwise they were to be fixed by reference to the price of an exact unbranded equivalent. One of the objects of the three-year period of freedom from control was to allow manufacturers to recover expenditure on research.

Earlier this year the Comptroller and Auditor General criticized the scheme in that it had not achieved the savings anticipated.[1] He found that the profits of pharmaceutical companies had been higher than those of general industry, and in particular the profit rates of British subsidiaries of American concerns "had consistently been much higher than those of general industry." The Ministry of Health and the Association of the British Pharmaceutical Industry replied to these criticisms, the latter pointing out that increased exports enabled a number of products to satisfy the test of reasonableness by reference to their prices overseas. In 1959 the value of drugs exported reached a record total of over £40m.

Among the main modifications of the existing voluntary price-regulation scheme which the Minister announced last week are the following. The Ministry may now call for direct negotiations about prices of drugs which are patent-protected and for which export prices may not be competitive. (The existing scheme allows for direct negotiation of prices only at the manufacturer's option.) The percentage of sales that must be exported before the export price test can be used is to go up from 20 to 25. The three-year period of freedom from control is no longer to be allowed to products which manifestly owe nothing to research. This last change is obviously an important one, but discussion on what "manifestly" means may lead to dispute. When announcing these modifications the Minister acknowledged the co-operation of the Association of the British Pharmaceutical Industry in the recent negotiations.

The scheme does not require disclosure of profit margins or of the cost of advertising (except where these may be factors in direct negotiation about price), but the A.P.B.I. have volunteered to provide additional information on these points. Commenting on the new agreement, Mr. Herbert Palmer, the president of the A.P.B.I., said that it reflected their desire to provide the Ministry of Health with acceptable evidence of the fairness and reasonableness of the prices charged for their products. He added that the wholesale price index for pharmaceutical products had risen since 1954 by only 1.01%, whereas that for all manufactured products had risen by 12.94%. Allowing for the fact that Britain's is a free economy, the A.P.B.I. and the Ministry have done well to reach a voluntary agreement on the continuation of a scheme which may not greatly have lowered the cost of the drug bill but which does seem to limit the opportunities of the few firms apparently ready to make excessive profits out of the medicinal treatment of disease.

[1] See *Brit. med. J. Supplement*, 1960, 1, 41.

SYNTHETIC A.C.T.H.

Within the last few weeks the synthesis of polypeptides with adrenocorticotropic activity has been reported from three separate sources. First in the field[1] was the group at the University of California under Choh Hao Li, who has been responsible for much of our knowledge of the chemistry of natural substances. They have synthesized a nonadecapeptide with an amino-acid sequence identical with that of the first nineteen residues from the NH_2-terminal of ovine, porcine, and bovine A.C.T.H. The product possesses an A.C.T.H. activity of 29–31 i.u./mg., approximately one-third to one-fifth the potency of the pure natural product; it also has melanotropic activity in frogs comparable to that of the natural hormone. The synthesis of the nonadecapeptide with glutamine instead of glutamic acid as the fifth residue from the NH_2-terminal was briefly reported in this communication; its biological activity was lower. The preparation of this latter compound has now been reported[2] by a team of Swiss workers from the Ciba laboratories in Basel, and they report that their "β^{1-19}-corticotropin-Glu^5-γ-amid" has corticotropic activity amounting to 20–30 i.u./mg. The third announcement[3] is available so far only in a newspaper report and a publication in scientific terms must be awaited before it can be evaluated. The statement is to the effect that a team of biochemists, under Dr. Klaus Hofmann at the University of Pittsburgh, has assembled twenty-three natural amino-acids to form "a substance identical, biologically, to the hormone A.C.T.H." This, it is asserted, "is the largest protein-like molecule ever synthesized." These syntheses confirm that less than half the natural molecule of 39 amino-acid residues can exercise the characteristic biological activity of the whole. It is too early to predict what will be the impact of these achievements on practical therapeutics. Clinical tests

[1] Li, C. H., Meienhofer, J., Schnabel, E., Chung, D., Tung-bin Lo, and Ramachandran, J., *J. Amer. chem. Soc.*, 1960, **82**, 5760.
[2] Schwyzer, R., Rittel, W., Kappeler, H., and Iselin, B., *Angew. Chem.*, 1960, **72**, 915.
[3] *New York Times*, December 3, 1960.

have not yet been made, and there is no evidence that the laboratory syntheses will lead the way to commercial processes. If something more than the "gram lots" spoken of in the press version of the Pittsburgh work becomes available, one more material would be presented to those engaged in trying to assay, in laboratory animals, by different methods and with different modes of administration, and in terms of a grossly impure standard, material for therapeutic use that is derived from any of three animal sources by a variety of processes. Whether such an event would be an advantage or not depends largely on how precisely defined and chemically identifiable the synthetic products may be; with seventeen or twenty-one centres of optical activity and multistage syntheses, hopes should not be pitched too high.

PROFOUND HYPOTHERMIA

Profound hypothermia was discussed recently at the Second World Congress of Anaesthesiologists in Toronto, and its dramatic possibilities received some notice in the press.[1] Comment on the method—devised by C. E. Drew[2] and his colleagues at Westminster Hospital about two years ago—has already been made in this journal.[3] By cannulating both atria and the left femoral and pulmonary arteries, cardiac by-pass is achieved; the extracorporeal circulation is passed through a heat-exchanger so that the body temperature can be lowered during induction or raised during emergence from hypothermia. Oxygenation is by the lungs of the subject. This notable British advance overcomes the limitation of surface cooling—at temperatures much below 30° C. cessation of cardiac activity is inevitable. With the new method, the circulation is not dependent on cardiac action because the pumps take over. Thus the body temperature can safely be lowered to 15° C. or even less. At this level periods of complete circulatory arrest up to one hour can be tolerated without brain damage; since the Westminster Hospital series now exceeds 80 cases, this claim can be taken as confirmed.

During the period of circulatory arrest there is a state of suspended animation, cardiac and respiratory functions are in abeyance, the E.C.G. and E.E.G. are inactive, the appearance and feel of the eyes and skin are cadaveric. This implies that death is not merely the cessation of function of "vital" organs: it is deferred until the depression of cell activity imposed by the hypothermia becomes irreversible upon rewarming. What the time limit may be of this reversible inhibition of biochemical dynamics remains to be seen. In humans periods exceeding one hour have been tolerated, and in dogs a report[1] mentions that a period of ten hours has been achieved.

The method has been tried successfully in other centres in Britain, France, the U.S.A., and elsewhere. One report[4] mentions brain damage in children, but it is apparent that in the unsuccessful cases the rates of cooling and rewarming were faster than those advised when the technique was originally described. The possibilities of the method have not yet been fully exploited: for example, restorative operations on the coronary arteries and the transplantation of organs now outside the scope of surgery may become technically feasible. Profound hypothermia protects the brain during operations on the heart, and it may come to serve a similar vital purpose during intracranial vascular operations.

[1] *The Times*, September 9, 1960.
[2] Drew, C. E., Keen, G., and Benazon, D. B., *Lancet*, 1959, **1**, 745.
[3] *Brit. med. J.* 1960, **1**, 565.
[4] Björk, V. O., *J. thorac. Cardiovasc. Surg.*, 1960, **40**, 237.

FOOD FOR THOUGHT

While the pleasures of the table are apt to be dwelt on at Christmas, a timely work published last week shows another side to the matter. People who want more—or fewer—calories in their food will find all the information they need to guide them through the present festivities in McCance and Widdowson's famous work,[1] issued by the Medical Research Council, now in its third and much-enlarged edition. The authors tabulate, for a great variety of foods, not only the calorie content per 100 g. but data on the content of protein, fat, carbohydrate, many minerals, and (in this edition for the first time) vitamins and amino-acids. The foods covered range from oysters to boiled beef, including on the way lobster and pale ale, apple-pie and porridge, port and ripe pheasant. The calorie content of a Christmas dinner comes out of the tables like this:

Food	Calories
Tomato soup, 200 g.	138
Roast turkey, 100 g.	196
,, potato, 100 g.	123
Brussels sprouts, 100 g.*	16
Bread sauce, 20 g.	22
Chestnut (stuffing), 20 g.	34
Mixed fruit pudding, 100 g.†	325
Dry sherry, 100 ml.	114
Champagne, 200 ml.§	148
Ruby port, 100 ml.	152
Coffee (black), 50 ml.	2
Total	1,270

* Boiled 30 minutes. † Recipe 606 (p. 14). § Vintage not specified.

Undoubtedly there are less frivolous uses to which this work can be put, for, as the authors say in their opening sentence, "A knowledge of the chemical composition of foods is the first essential in the dietary treatment of disease or in most quantitative studies of human nutrition." Despite its tabular presentation, this is a book which draws the reader on from page to page. Though hardly fireside reading, it is an indispensable work of reference.

We record with regret the death on December 16 of Sir Ernest Finch, a vice-president of the Royal College of Surgeons and formerly professor of surgery at the University of Sheffield.

[1] McCance, R. A., and Widdowson, E. M., *The Composition of Foods*. Medical Research Council Special Report Series No. 297. H.M.S.O. 1960. 30s. net.

Clinicopathological Conference

A CASE OF RAPID MENTAL DETERIORATION

DEMONSTRATED AT THE

POSTGRADUATE MEDICAL SCHOOL OF LONDON

This is the case of an elderly man who was admitted to Hammersmith Hospital on account of a rapid mental deterioration, muscular weakness, and incoordination (Case No. 232,146 ; P.M. No. 8,959).

Clinical History

DR. C. L. COPE: The patient was a grocer with his own shop, who at the time when he came in was 66 years old. It was difficult to get a history from him, for reasons which will appear, and we had to get most of it from his wife. In 1949 he had a partial gastrectomy for ulcer and had had no real gastric symptoms after that. In January, 1959, he had an attack of acute bronchitis and it is, I think, relevant that he recovered well from this and continued without recurrence of bronchitis right through the summer. In July, 1959, his wife noticed that he could no longer add up the customers' bills properly in the shop, and he made other mistakes. Within a month this had got worse and he became quite incapable of helping in the shop and unable to remember anything very clearly. Then there began general muscular weakness, particularly affecting the legs. He became incoordinated, which showed itself as an inability to shave himself, and towards the end of the month (August) he was unable to stand properly. He began to get considerable swelling of his legs and ankles about three weeks before his admission into Hammersmith Hospital on September 4, 1959.

ON EXAMINATION

When he came in he was quite unable to give a clear history, but knew his own name. He did not know where he was, he didn't know the day or the time of day, and we could get very little out of him. He would obey simple commands, but only when they were very forcibly expressed, and he was quite unable to concentrate in any way at all. There was no complaint of headache or vomiting. Before he came he had had one attack of violent behaviour, but we don't know the details of that. There were no fits and there was no true unconsciousness. He had a drowsiness rather than a true coma. There was no incontinence. He was wasted and ill-looking and his wife thought that he had lost a good deal of weight recently. He was unable to move without help ; partly because of muscle weakness, partly because of incoordination, and partly because of lack of urge, owing to this semi-comatose state. His pulse was slightly up but regular. Blood-pressure was normal ; jugular venous pressure was not raised. There was a suggestion at that time of early clubbing. His temperature was not raised, and I think that is an important point. No signs of any significance were found in the heart or lungs. On his abdomen there were rather markedly prominent abdominal veins with the flow upwards. The liver was enlarged 3 in., firm and smooth but not tender. No free fluid could be detected in the abdomen. The spleen could not be felt and the kidneys were not palpable. So the only abdominal findings were these veins and an enlarged liver. He had gross oedema of the left leg to the knee and of the right leg right up to the thigh ; soon after coming in, this oedema spread right up into the abdomen, remaining more marked on the right side of the abdomen and buttock than on the left. The asymmetrical oedema was not explained by his posture. In the central nervous system he had the mental changes which we have already noted, but no abnormality was found in the cranial nerves. His speech, in so far as he was willing or able to speak, seemed fairly good. Sensation and tone and power were extremely difficult to analyse because of his state, but nothing positive was got out of that and there was no certainty then or later that there was any sensory disturbance, or alteration of muscle tone. Tendon reflexes appeared to be equal and normal, but the left plantar was extensor. The right one was then flexor. In the fundi there was a suspicion of very early papilloedema, but that was by no means certain. The neurologist, Dr. Pallis, considered there was none. There was old choroiditis in the right fundus and a large, much more recently developed, resolving haemorrhage in the vitreous of the left eye. There was no albumin and no sugar in the urine.

Here then was a man with rapid mental deterioration with an upgoing toe and with general malaise. The strong probability was a secondary in the brain and a primary in some part of the body as yet undetermined. Much of the later story revolves round the hunt for the primary.

INVESTIGATIONS

The special investigations that were done were limited by his progressive deterioration, and some of potential diagnostic value could not be completed. His sedimentation rate was not grossly raised at 12 mm. The total serum proteins were 7.3 g. with 2.4 albumin and 4.9 globulin. There was an α_2- and β-globulin pattern which, in the absence of albuminuria, suggests a neoplasm. The Wassermann and Kahn tests were negative ; haemoglobin was 87% with a normal haemoglobin concentration in the cell. A blood count showed 17,000 white cells, which should be noted because it is of significance. There was a normal differential—76% neutrophils, 24% lymphocytes. The occult-blood test was negative. Liver-function tests were essentially normal. A possible place for a primary was the pancreas, but a serum amylase was normal. The prostate felt reasonably normal and the acid phosphatase was not high enough to be significant. Other possible places for primary neoplasm were the kidneys or a bronchus. In the chest there was some scarring in the middle lobe and there is a note that on the left side "the hilum is not entirely beyond suspicion" (Fig. 1). especially in the lateral (Fig. 2). Tomograms produced no evidence of a neoplasm and no further significant information was derived as to the nature of the possible node in the hilum. That again may be significant. In the skull there was no bony lesion. The pineal was central. An intravenous pyelogram showed that there was a fairly well functioning right kidney, but no

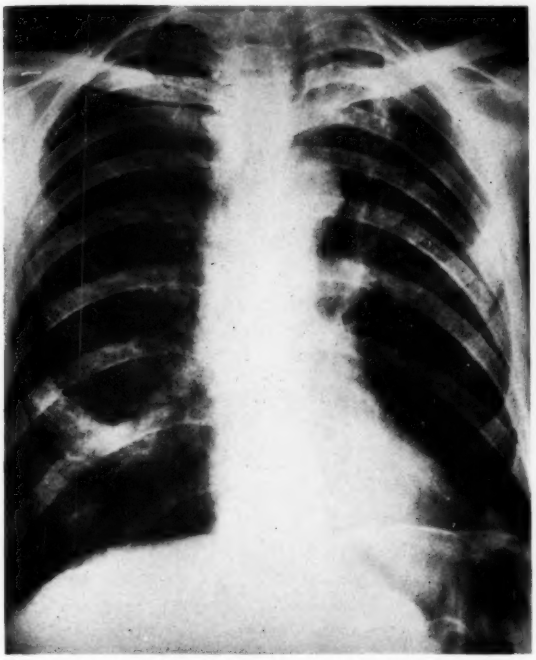


FIG. 1

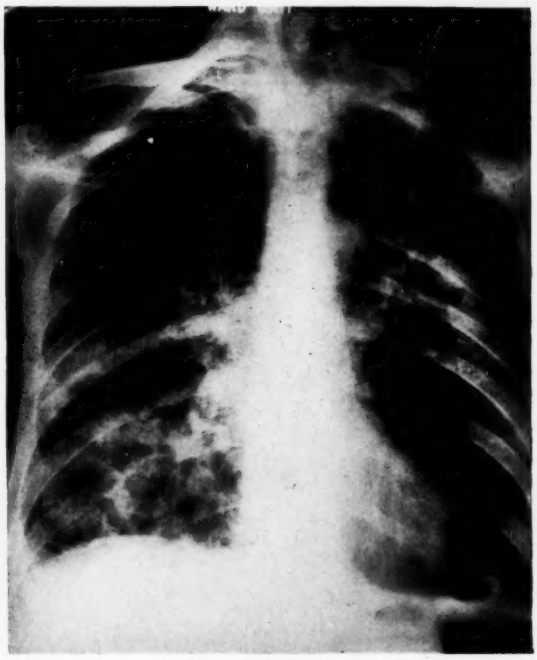


FIG. 3

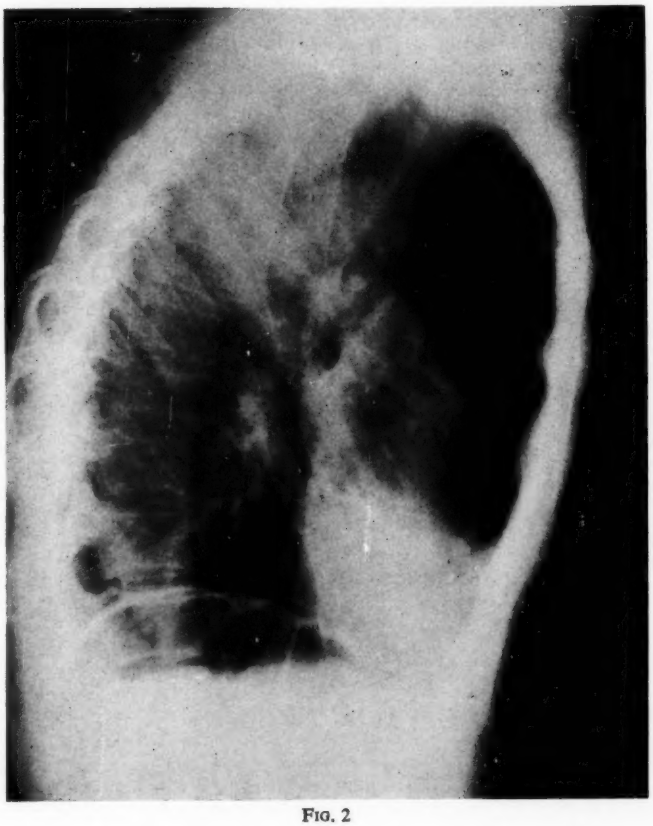


FIG. 2

FIG. 1. — Chest radiograph showing scarring in right middle lobe and ? abnormal shadow in left hilum.

FIG. 2.—Lateral view of chest, showing partial consolidation of right middle lobe.

FIG. 3.—Chest radiograph in terminal stage showing areas of consolidation.

FIG. 5.—Metastasis in hilar lymph node showing well-differentiated tall clear cells forming papillary and glandular structures. (×100.)

FIG. 6.—Edge of cerebral metastasis with cerebral tissue below and solid, poorly differentiated adenocarcinoma at the top of the picture. (×100.)

FIG. 7. — Recent abscess in kidney. (×100.)

FIG. 8.—Bland thrombus in inferior vena cava undergoing organization. The smooth muscle of the wall is seen above and to the right. (×100.)

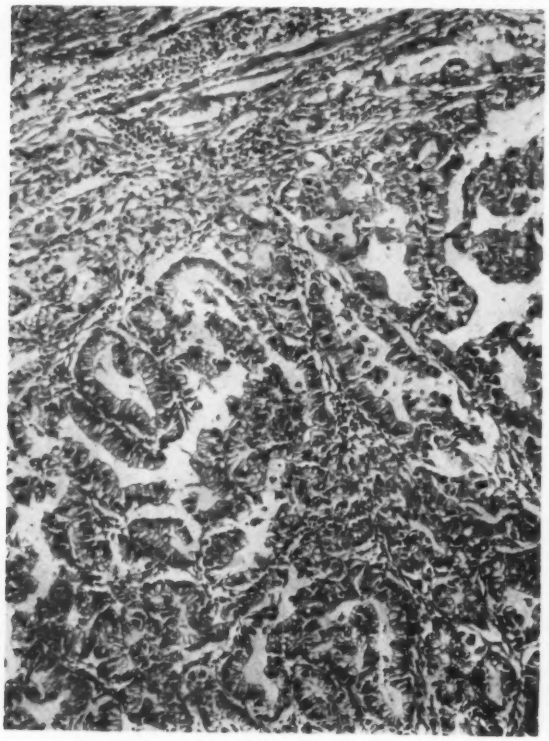


FIG. 5

FIG. 6

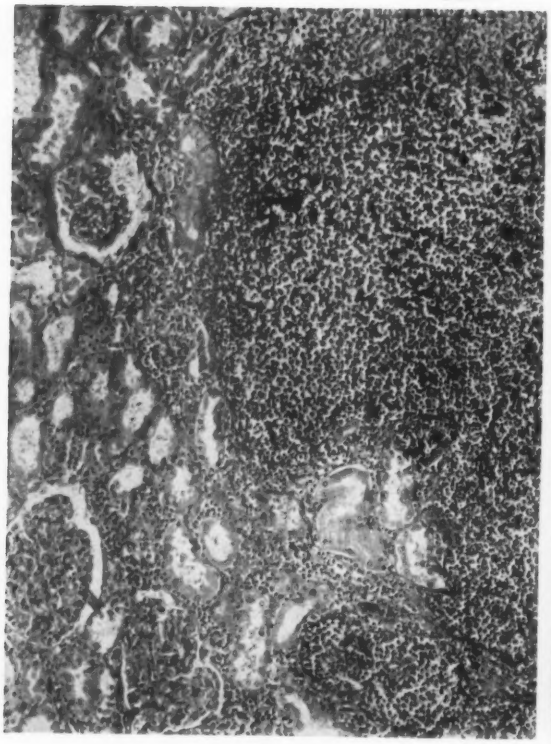


FIG. 7

FIG. 8

function at all in the left kidney. Later a retrograde pyelogram showed a perfectly normal left renal pelvis.

Whilst these investigations were going on, the veins on the patient's abdomen had become much more obvious and it was now quite apparent that he had in fact got an inferior vena caval thrombosis. The veins on the abdomen not only became more dilated but they varied quite considerably from day to day in their size and even position, and new ones came and old ones changed. An E.E.G. had confirmed that there was abnormality in the left central and precentral regions, almost certainly due to a structural lesion. The cerebrospinal fluid was normal.

It then became apparent that he had some sepsis in the right foot. This had possibly been missed previously because he had very gross oedema of the whole of that leg and the actual reddening that was present was very slight indeed. There developed a lymphangitis and a tender inguinal lymph node on the right side for a few days. He was given antibiotics at this time with improvement in the local sepsis and subsidence of the inguinal tenderness. A blood culture was done towards the end of September. The result was negative, but he had then been on antibiotics.

TERMINAL ILLNESS

On September 23 he developed suddenly and for the first time a pronounced albuminuria, and this occurred at a time when his blood urea had fallen from 70–100 mg./100 ml., which it was when he came in, down to 40–50 mg. His general condition was continuing to deteriorate. He was rapidly becoming too ill for further investigations. Both plantars had now become extensor, but there were still no more definite lateralizing neurological signs. The fundi were still unchanged except for some resolution of the haemorrhage. At this stage, for the first time he developed a light fever of around 99–99.5° F. (37.2–37.5°C.). Till now he had been afebrile. The white count had now risen from 17,000 to 21,000, with 90% polymorphs. It was quite clear that there must be a pyogenic infection somewhere, but we did not know where. He then developed crepitations at the right lower lobe and these became progressively more marked during the next few days. His general condition continued to deteriorate. He became incontinent of urine and faeces and, finally, completely comatose. Neither a bronchogram, a cerebral arteriogram, nor a barium meal was done.

In this terminal stage he had developed some consolidation of the middle and lower zones in the right chest and some also on the left side (Fig. 3). His blood-pressure, which had been well sustained until now, fell to 60/40. He developed a peripheral shock-like state. His blood urea rose again to 121 mg., and the fever, which had tended to subside for two or three days, recurred again up to about 100° F. (37.8° C.). His pulse rate increased; his white count continued to rise to 28,000. The rales continued to develop in his chest, and he died on October 6.

Clinical Diagnosis

(1) Terminal bronchopneumonia.
(2) Inferior vena caval thrombosis.
(3) ? Septic thrombophlebitis.
(4) Thrombosis of the left renal vein.
(5) Secondary neoplasm in the left frontal zone.
(6) ? Secondary deposits in the liver.
(7) Old partial gastrectomy.
(8) A primary tumour, the nature of which had not been determined.

Post-mortem Findings

DR. J. AZZOPARDI: Necropsy was performed 22 hours after death. Externally, this thin, elderly man showed gross pitting oedema of both lower limbs, extending to the groin on the right side and up to the lower part of the thigh on the left.

Both *pleural cavities* were largely obliterated by fibrous adhesions. The *right lung* weighed 1,110 g. (normal, 450 g.). It contained scattered, small abscesses and septic infarcts in all lobes but affecting chiefly the lower lobe. They averaged 1 cm. in diameter and had an opaque, yellow centre fringed by a red, congested zone. A septic infarct in the subapical region of the upper lobe measured about 6 by 4 cm. Many pulmonary arterial branches, especially in the lower lobe, were blocked by emboli. These varied in colour from red-brown to orange-yellow. The *left lung* weighed 620 g. (normal, 400 g.). It contained a small number of similar abscesses. A more or less rounded (2-cm. diameter) lesion in the lateral basal segment of the lower lobe had a firm whitish appearance suggestive of tumour. Microscopical examination of both lungs showed pyaemic abscesses whose appearance suggested only a few days' duration. The presence of thrombi in the pulmonary arteries, undergoing organization, was confirmed. The lesion in the left lower lobe was a bronchial adenocarcinoma (Fig. 4), moderately well differentiated and with slight intracellular production of mucin. Some anthracotic scar-tissue was present at the centre of the

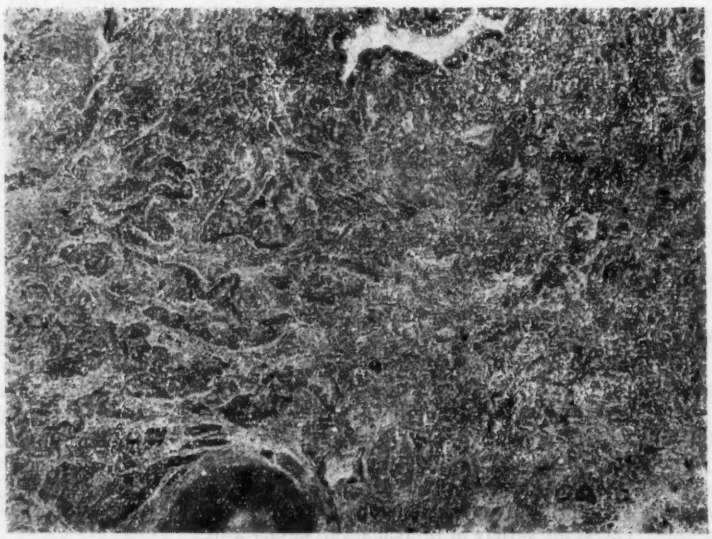


FIG. 4.—Low-power view of primary tumour in lung showing malignant acini surrounding bronchi and infiltrating fibrous tissue. (×40.)

lesion. One left hilar *lymph node* was enlarged and replaced by firm white tissue. Microscopically (Fig. 5) it contained rather papillary metastatic adenocarcinoma. The *brain* weighed 1,310 g. (normal 1,400 g.). A solitary rounded mass, 2.5 cm. in diameter, was present on the inferior aspect of the left frontal lobe, about 4 cm. from the anterior pole of the hemisphere. It was situated in the white matter and extended almost to the cortical surface. It was firm, white, and homogeneous, and clearly demarcated from brain tissue. Microscopically (Fig. 6) it consisted of more or less solid, poorly differentiated, adenocarcinoma with a necrotic centre.

The *kidneys* (right=170 g., left=190 g.; normal, 170 g. each) had capsules that stripped easily, leaving a generally smooth cortical surface studded with small abscesses. Renal arteries and veins normal. Microscopically (Fig. 7) the kidneys showed scattered abscesses of about the same age as those in the lungs. The intervening parenchyma was normal. No micro-organisms were seen in the kidneys or lungs. The whole of the inferior *vena cava* was thrombosed to just above the level of the renal veins. The thrombus was lightly adherent to the vein wall. Thrombus filled both common iliac and both external iliac veins. This thrombus did not contain any pockets of pus or other signs to suggest sepsis. Microscopically (Fig. 8) there was organizing thrombus in the vein without evidence of inflammatory reaction. The *heart* weighed 280 g. (normal, 320 g.). Its chambers and valvular orifices were normal. Mild non-obstructing coronary atheroma only. Microscopical examination showed normal myocardium. The *aorta* showed confluent atheroma in its abdominal portion, with a calcified shell encasing the area of the bifurcation.

The *general peritoneal cavity* was normal. A partial gastrectomy had been carried out. Normal gastroenterostomy stoma. Alimentary tract normal. Adhesions around the site of the old appendicectomy operation. The *liver* weighed 1,565 g. (normal, 1,600 g.) and, apart from some pallor suggestive of fatty change, appeared normal. No metastases present. A cavernous haemangioma was present on the anterior surface of the right lobe. Microscopical examination showed moderate fatty metamorphosis, not restricted to any zone of the lobule, and confirmed the presence of a cavernous haemangioma. The *spleen* was small, weighing 78 g. (normal, 170 g.). The pulp was normal. The appearance was not that of a septic spleen. Microscopically it appeared normal. Both *adrenals* were slightly overweight, together weighing 19 g. (normal, 14 g.). *Pancreas, biliary tract, prostate* and other organs normal.

Pathologist's Diagnosis

(1) Peripheral adenocarcinoma left lower lobe lung. Metastases in a left hilar lymph node and left frontal lobe of brain.

(2) Inferior vena caval thrombosis (?due to carcinoma bronchus). Oedema lower limbs.

(3) Terminal pyaemia with pulmonary and renal abscesses. Pulmonary arterial emboli.

(4) Old partial gastrectomy and appendicectomy. Cavernous haemangioma of liver. Fatty liver.

The primary bronchial adenocarcinoma was peripheral and not arising from a nominate bronchus. The vast majority of adenocarcinomata are peripheral in this sense.[1] This is the variety of bronchial carcinoma which has an equal sex distribution and which is not related to smoking or other known environmental factors. Brain metastases in bronchial carcinoma are found at necropsy in up to 40% of cases. About 5 to 10% of all patients with bronchial carcinoma are said to present clinically because of neurological symptoms.[2] The metastases are cerebral in two-thirds of the cases and cerebellar in the other third; this indicates a predilection for the cerebellum since this relative incidence is out of proportion to the relative sizes of the two parts. In 20 to 30% of cases brain metastases are solitary on gross examination. In general, metastases to the brain are believed to reach it by way of the blood-stream. Recently Onuigbo,[3,4] studying metastases in bronchial carcinoma, found that metastases to the adrenals and brain were more often ipsilateral than contralateral in a ratio of approximately 3:2. Because of this and some other supporting evidence he suggests that retrograde lymphatic spread plays an appreciable part in the development of cerebral metastases. While there are no lymphatics in the brain, he stresses the existence of communications between lymphatic pathways and the subarachnoid space and perivascular spaces in the brain. The factual findings on which this hypothesis is based need confirming, however.

The caval thrombosis could have been due to various factors. One distinct possibility is that this is an example of the venous thromboses that are associated sometimes with carcinoma, especially carcinoma of the pancreas and bronchus. Among the other unexplained associations with bronchial carcinoma, one might mention peripheral neuropathy, and, more rarely, the development of a Cushing-like syndrome.

Discussion

Dr. COPE: If we can just review the story from the clinical side briefly, you remember there was an attack of bronchitis in January, 1959, which cleared up. It is possible, in retrospect, that that was in some way related to this peripheral carcinoma, but it did clear up sharply and no symptoms occurred for six months thereafter. The first presenting feature was this neoplasm in the brain, and after that, so far as we can gather, occurred the inferior vena caval thrombosis. I must confess that this influenced me quite considerably. I thought it was highly probable that it was associated with carcinoma of some form in or near the vena cava itself, and it was for that reason that we investigated first the kidney for hypernephroma and the pancreas as far as we could go, which wasn't very far. We got no positive evidence from those investigations, but I still felt, myself, that there was a possibility of carcinoma in the abdominal lymph nodes even if there was none in actual organs in the abdomen. A carcinoma in the bronchus was, we thought, probably excluded by the *x*-rays. That, I think, is a point which we might discuss further, when Dr. Steiner has seen these films. I think, if I remember rightly, in the first lateral film done when he came in, there are changes which might link up with this peripheral nodule which was found post-mortem, but it's easier to say that after the event than before.

Why he got this thrombosis in the inferior vena cava is another point about which I think we may well not reach a conclusion. A thrombotic tendency, as Dr.

[1] Walter, J. B., and Pryce, D. M., *Thorax*, 1955, **10**, 117.
[2] Halpert, B., Erickson, E. E., and Fields, W. S., *Arch. Path.*, 1960, **69**, 93.
[3] Onuigbo, W. I. B., *Brit. J. Cancer*, 1957, **11**, 175.
[4] —— *Brit. J. Tuberc.*, 1958, **52**, 141.

Azzopardi has said, is particularly liable to occur in certain forms of carcinoma, but thrombosis of the inferior vena cava "out of the blue" is an extreme form of thrombotic tendency and would be a very unusual development without some local cause. I think it is quite likely that the chain of events was that, after he got the mental deterioration, he developed a septic foot; that because of this mental deterioration he didn't do anything about it or mention it and that sepsis ascended through the lymph nodes unrecognized either by us or by his wife and started the inferior vena caval thrombosis, but that's speculative and there may be other possible explanations.

RADIOLOGICAL APPEARANCES

Dr. R. STEINER: It is rather a disappointment because we suspected this nodule near the hilum. On the left lateral film (Fig. 2) one can see a shadow made up by the vascular pattern of the hilum quite clearly, and then, below this, a small, round lesion and behind it another shadow. In retrospect one could suspect two lesions: one in front in the region of the lingula, which is not absolutely clear, and then at the back, superimposed on the spine, there is a small nodule. As Dr. Cope says, it's easy in retrospect when we know now where the tumour was. But if you suspect a hilar lump, and no doubt there was a node there, then these peripheral lesions are significant. We took tomograms of the hilum and the sections were made in the antero-posterior plane. Seeing the films again, and had the man been fit enough and reasonably co-operative, we should probably have done a lateral tomographic cut to get at the root shadow and possibly also the peripheral lesions which are partially obscured. By this means it would have been possible to pick up either lesion. I am still not quite clear where the primary was. One question I should like to ask is how much infection was there in this nodule?

Dr. AZZOPARDI: In the left lung?

Dr. STEINER: In the left lung. Was it all tumour or was there also infection?

Dr. AZZOPARDI: That particular nodule was all tumour.

Dr. STEINER: So that the nodule which you saw and which one can see on the film was actually tumour?

Dr. AZZOPARDI: Yes.

Dr. STEINER: And where exactly was it?

Dr. AZZOPARDI: In the lateral basal segment of the left lower lobe.

Dr. STEINER: The lesion in the lingular area is probably infection.

Dr. AZZOPARDI: Yes, that probably was infection.

Dr. STEINER: Clearly on the film alone it would be very difficult to pick any individual lesion and say, "This is a tumour." It would be quite impossible.

Dr. COPE: Even in retrospect?

Dr. STEINER: I should have thought so. The only thing we could have done, as I already said, was to take tomograms in the lateral plane and pick up the node, and that would also have picked up the lump in the lung. On the antero-posterior film you wouldn't suspect anything; there is nothing to see except for the hilum, which is a little larger than one would expect it to be.

Dr. COPE: Is that a nodule near the apex of the heart?

Dr. STEINER: This shadow? I think one would have called it normal.

ORIGIN OF THE THROMBOPHLEBITIS

Dr. COPE: One question I should like to have had an answer to was how this thrombophlebitis was caused. Dr. Azzopardi said that the abscesses at the end were of a few days' duration only, probably, and that they were sterile. The patient had antibiotics right through that period, so the organisms presumably had died off as soon as they got to the abscess areas. It seems a peculiar bit of pathology to me, if it was a sterile abscess.

Dr. AZZOPARDI: The pus from the abscesses wasn't cultured, so perhaps it's not fair to say that they were sterile. I didn't see any bacteria in the microscopical sections, but that is slightly different from saying that they are sterile.

Dr. COPE: Now, was there an abscess, or was the pus actually in the clot in the inferior vena cava?

Dr. AZZOPARDI: No, there was no sign of any inflammatory reaction in the thrombus in the inferior vena cava or in the wall of the inferior vena cava.

Dr. COPE: But that is the presumptive site of these abscesses, the origin of them?

Dr. AZZOPARDI: Certainly I think the thrombus in the pulmonary arteries, and so on, came from there. Where the bacteria came from is much more difficult to decide. I don't really know whether the cellulitis in the foot was secondary or whether it had been present there all the time and had caused an ascending infection that led to thrombosis of the inferior vena cava. If that is so, then this must have happened at a very early stage and he must have had the cellulitis in his foot when still at home.

Dr. COPE: It is possible that he did, although it was probably of mild degree then and he was afebrile at that time. Now you made the distinction between septic infarcts in the lung and small abscesses. Is that because you know that there were thromboses?

Dr. AZZOPARDI: Yes, I think only because there was this great mass of thrombus in the inferior vena cava, which I presumed was the source of the thrombi in the pulmonary arteries. We thought that the origin of the abscesses was on a basis of: emboli, infarction, and infection.

SKIN DISEASE AND CANCER

Dr. COPE: There is one other unusual association I should like to mention among the queer things that are associated with bronchial carcinomas. We have had two or three examples lately of atypical skin disorders, especially of the pemphigoid type. We have had two recently which were diagnosed confidently by skin specialists as pemphigus, and I gather dermatologists recognize the association with bronchial carcinoma.

Dr. AZZOPARDI: Is it more than coincidental?

Dr. COPE: They think so.

Dr. AZZOPARDI: Is it any particular variety of carcinoma of the bronchus from the histological point of view? Or does it apply to any type?

Dr. COPE: I don't know.

Dr. AZZOPARDI: Why I ask that is because many of the less common disorders occurring with bronchial carcinoma, e.g., Cushing's syndrome, have been associated with oat-cell carcinomas.

Professor RUSSELL FRASER: There is an association of dermatomyositis with cancer; it isn't only with bronchial carcinoma. You get it with ovarian carcinomas and, in fact, carcinomas in general.

RENAL FUNCTION

Dr. J. SHILLINGFORD: In retrospect, is the poor filling of the kidney on the left an artefact, or is it thought to be associated with renal vein thrombosis?

Dr. STEINER: We really suspected at the time a renal vein thrombosis. After 40 minutes, and this is a 40-minute film, you would expect some contrast excretion on the left side; the right side looks very normal. So at that time we assumed that there was some obstruction in the venous return of the left kidney. Dr. Azzopardi, was the left kidney swollen? Was there any evidence of a collateral circulation on the surface of the kidney?

Dr. AZZOPARDI: The left kidney was slightly enlarged, but then this was only very slight and was presumably associated with the oedema that is found along with pyaemic abscesses. Certainly the renal veins themselves were perfectly all right, but, of course, there was a functional block in so far as the inferior vena cava was thrombosed. Why the left kidney didn't function at that time I don't know, because it is unlikely that the inferior vena cava was blocked at the level of the left renal vein and not the right, unless the entry of the left renal vein was anomalous in this case and was lower than the right.

Dr. STEINER: But the block may have been partial at that time and was only affecting the left side and not the right.

Dr. COPE: It would appear possible that it was incomplete for a time because it is of interest that the appearance of the albuminuria for the first time quite clearly coincided with a fall, not a rise, in blood urea.

LIMITATION OF THROMBOSIS

Dr. M. MILNE: I think first of all there is no evidence whatsoever here that the thrombus in this cava is infected. It looked a perfectly innocent thrombus to me and I would take the view that it is a thrombus directly secondary to the carcinoma. Now, of course, this does not start in the inferior vena cava. It starts in small venules either in the leg or in the pelvis and spreads upwards. There is nothing really, once it has started spreading, to check it until it gets to the renal veins, because that is where you get a very large inflow of blood into the vena cava, and I think this was the picture when he was first seen: he had the signs of inferior vena caval obstruction but no evidence of renal vein obstruction. After that, presumably the left kidney was obstructed first as the clot moved upwards, causing reduced function of the left kidney, with some proteinuria, but completely normal functioning of the other kidney, and therefore there was no reason for the blood urea to go up.

Dr. COPE: This isn't what happened. It was the other way round. You see, at the time when there was no albuminuria the blood urea was over 100; when the albuminuria appeared the blood urea was dropping.

Dr. MILNE: But after that it certainly went up terminally when both renal veins were obstructed. Dr. Azzopardi said that thrombophlebitis from carcinoma is less common in the case of the bronchus than in carcinoma of the pancreas. I disagree very strongly with this. It is less common per single case of cancer, but much more common per unit of population.

Dr. AZZOPARDI: This is what I meant, less common per cancer, not per population.

Dr. MILNE: Per population bronchial carcinoma is by far the commonest cause of this association and really the clinician is more concerned with per population than per cancer. The other point is that very often these secondary thromboses are associated with marked globulin changes such as this man had. I think that changes in plasma-protein pattern have something to do with this clotting tendency in carcinomata, and one protein in plasma which we often neglect is the fibrinogen. Increase of fibrinogen has been put forward recently as one theory for clotting of renal veins in amyloid disease, and I think in future we should perhaps do estimations of fibrinogen as well as of other globulins when we find this clotting tendency in association with cancer.

Dr. COPE: I am not quite happy about the reason expressed for the thrombosis stopping at the renal veins being because that is the first point where blood in quantity comes into the main flow. Surely the first point where blood comes in is at the junction of the iliacs where the main venous blood from the other leg come in. We have got to assume, if Dr. Milne's argument is true, that thrombosis started in both legs—the septic one and the one which wasn't septic, which seems unlikely.

Dr. MILNE: Well the actual flows as measured by the P.A.H. method[a] are 30% of the resting cardiac output below the renal veins. This means that approximately 15% is coming up each common iliac vein. I agree that that is one point where a clot may stop and then, of course, it does not affect the vena cava at all. Once, however, it is past the junction it usually extends to the renal veins, where 20% of the resting cardiac output is entering the vena cava. After that, another point where it may stop is at the site of entry of the hepatic veins where about 25% of the resting output is entering. Very, very rarely does a clot extend further than the entry of the hepatic veins into the vena cava. But these are selected points where a clot can end simply because of a rapid inflow of blood which seems to help to delay clotting, presumably by sealing off areas from the advancing clot.

GLOBULIN PATTERN

Dr. AZZOPARDI: Dr. Milne, could you enlarge on the quoted statement that a high α_2- and β-globulin is suggestive of carcinoma. How reliable is it, and are there other conditions which can do that?

Dr. MILNE: Well, this is rather a distinctive plasma-protein pattern. It occurs in a lot of conditions, I agree. It is perhaps most typical of the nephrotic syndrome. Of course here this is excluded—there was no proteinuria when the α_2- and β-globulin pattern was first found. Secondly, it does occur in advancing diabetes with vascular changes, before the renal lesion occurs. And thirdly, it occurs in amyloid, again sometimes without proteinuria. Well, all these seemed unlikely. The other big association is carcinoma. To give an example, Professor Sheila Sherlock has used it as an indication in cirrhotics of primary liver cancer because this is quite unlike the pattern one gets in typical uncomplicated

[a] Grossman, J., Weston, R. E., Rubler, S., Horowitz, H. B., Wolfman, M., and Leiter, L., *Fed. Proc.*, 1955, **14**, 64.

cirrhosis where there is a high gamma globulin. So that I think that statistically in a case like this, with no other cause for this pattern and where there was certainly strong clinical suggestion of cancer, it is further suggestive evidence. That is as far as I would go.

Professor RUSSELL FRASER: Rather like the sedimentation rate, perhaps, in that respect?

Dr. MILNE: Comparable.

We are grateful to Dr. J. P. Shillingford and Dr. B. E. Heard for assistance in preparing this report, and to the photographic department of the Postgraduate Medical School for the illustrations.

MEDICINE IN CHINA

An interesting talk on medicine in China was given by Dr. HSUEH KUNG-CHUO at the London School of Hygiene and Tropical Medicine on December 12. Dr. Hsueh Kung-Chuo is the vice-president of the Chinese Academy of Medical Science, which might be described as a counterpart in China of the National Institute for Medical Research, and he is visiting this country with other medical experts from China at the invitation of the Royal College of Physicians.

Dr. Hsueh Kung-chuo, who spoke through an interpreter, said that the "patriotic health campaign" in China had centred round the extermination of four pests—rats, bed bugs, flies, and mosquitoes—and the prevention, treatment, and eradication of diseases which had constituted the most serious menace to the health of China's 650 million population. To date, the four pests had been considerably reduced and some diseases had been eradicated, while others were under control. There had not been a single case of cholera in the past 11 years, and smallpox and bubonic plague had been basically eradicated. Further, owing to improved sanitation and hygiene there had been no infectious diseases at all in certain areas.

Traditional and Western-style Medicine

Chinese medicine and pharmacology dated back to antiquity and was the crystallization of the experience accumulated by the Chinese people over thousands of years of struggle against disease. In the China of old, said Dr. Hsueh Kung-chuo, its ruling classes, indifferent to the sufferings of the people, persevered in a reactionary policy of wiping out traditional medicine, thereby causing irreparable loss. Since the foundation of the Chinese Peoples Republic, the Chinese Communist Party had laid down a policy of uniting traditional and Western-style medicine. Colleges and schools of traditional medicine were established in many provinces and cities, and a system under which students served apprenticeships with traditional physicians had done much towards training medical personnel. At present traditional and Western-style medical practitioners worked side by side in all hospitals. To date more than 2,000 Western-style medical workers were studying traditional medicine on a full-time basis, and many more were studying part-time. The integration of traditional and Western medicine had yielded many new results in clinical practice and research in basic sciences. For example, in the treatment of hypertension, diabetes, chronic arthritis, etc., the combined therapeutic methods from the two schools of medicine had considerably shortened the course of treatment. Again, traditional drugs and acupuncture were used in the treatment of acute appendicitis and other complaints in addition to surgery.

Hospital and Communal Care

Curative health institutions in China had been developed to implement the policy of serving production and accommodating the masses. They had therefore been developed in rural areas as well as in cities. That was a fundamental change from the irrational pre-liberation situation when medical services served only a selected minority, said Dr. Hsueh Kung-chuo. At the end of 1959 the number of health institutions reached 390,000—a hundred times the number in 1949. The policy of the curative medical service was to serve the 650 million people, giving equal attention to the urban and rural populations.

Since the establishment of the people's communes, a system of collective medical care had been practised. Each member of the commune paid a nominal fee annually which entitled him to free medical care. The balance was made up by the State and the commune welfare fund. Great concern had been shown by the Chinese Communist Party for the health of the national minorities, and intense efforts had been made to develop a health service in the national minority areas. At the end of 1959 the number of medical and health service institutions in those national minority areas totalled 54,000. The medical and health personnel totalled 219,000.

Quoting some specific examples of advances made in combating disease, Dr. Hsueh Kung-chuo stated that in the years 1950 to 1958 the mortality rate from dysentery had been reduced by 90%. In the case of toxic bacillary dysentery the administration of traditional drugs in conjunction with antibiotics had succeeded in bringing down the mortality of the disease from 25 to 4.2%. In the treatment of pulmonary tuberculosis excellent results had also been obtained by combining the intrabronchial and intracavitary administration of antibiotics with traditional drugs, acupuncture, and breathing therapy. So far as the treatment of cancer was concerned, the Chinese medical practitioners used irradiation therapy, surgery, and combined traditional and Western therapy. Of 1,562 cases of oesophageal cancer treated surgically, the mortality rate was 10%.

Maternity and Child Welfare

The Chinese Communist Party attached great importance to maternal and child health, continued Dr. Hsueh Kung-chuo, and at the end of 1959 the number of maternity and child health centres was 200—more than twice the number which existed in 1949. The number of regular beds was 7,900, four and a half times the number in 1949. There were 30 hospitals for children with 4,000 regular beds. Since liberation the State had trained large numbers of midwives and had popularized modern delivery methods. As a result, the incidence of puerperal fever had been greatly reduced. Large numbers of child-care workers had been trained, and scientific methods of child care had been brought to the masses. The incidence of infectious diseases among children had been markedly reduced. Chinese labour-protection regulations laid down that women were entitled to 56 days' maternity leave with full pay and full medical care during childbirth, and special consideration from the point of view of work before and after childbirth. For instance, in agricultural areas no heavy work was done during pregnancy, women with infants did not work far from their homes, and women who were menstruating were not allowed to work in water. In 1959 some 48 million children were in the care of nurseries run by the rural communes.

Medical Education

Dealing with medical education, Dr. Hsueh Kung-chuo said that medical and pharmacological colleges and schools had been established in all provinces, cities, and autonomous regions. Up to the end of 1959 the number of medical and pharmacological schools was 93,000—more than seven times the pre-liberation figure. In addition to the standard five-year medical course, six- and eight-year courses were

introduced into the curricula in 1959 in order to train research workers and teachers. There were also part-time courses, and at present some 200,000 students were receiving part-time education in medical and pharmacological colleges. Furthermore, various types of training courses had been instituted to raise the standard of traditional and Western-style medical workers. During the past three years more than 48,000 had graduated from medical colleges. Up to the end of 1959 the number of traditional and Western-style medical personnel was 1,460,000, of which 86,000 were Western-style physicians, 400,000 intermediate-grade health workers, 500,000 traditional practitioners, and 400,000 junior-grade health workers. In addition there were a large number of part-time health workers. For the past eleven years, continued Dr. Hsueh Kung-chuo, the Chinese Peoples Republic had been implementing a policy of gearing scientific research to the immediate needs of socialist construction, and closely integrating theory with practice.

Turning to the question of pharmaceutical products and medical appliances, Dr. Hsueh Kung-chuo said that before liberation China depended almost entirely on the import of drugs, with the exception of traditional drugs, and appliances. However, as the result of the great development of those two industries, domestic production now supplied 90% of the national demand.

TESTING DRUGS IN MAN

STEPHEN PAGET MEMORIAL LECTURE

The Research Defence Society met on December 6 at University College, London, to hear the 29th Stephen Paget memorial lecture by Professor J. H. BURN, F.R.S. His subject was "The Testing of Drugs in Man." This is the yearly occasion on which a reasoned reply is publicly given to antivivisection propaganda. The meeting was under the chairmanship of the society's president, Lord HALSBURY, and was attended by a considerable number of guests. Dr. J. M. WALKER, of Oxford, read the lecture, as Professor Burn was absent through illness.

After a brief review of the working of the Act of 1876, which controls experiments on animals in Britain, Professor Burn proceeded to consider the ways in which new drugs may be tested in man and some of the pitfalls in so doing. He was concerned mainly with the proper use of the placebo in such trials. Large-scale trials had shown, he said, that about 35% of those suffering from such varied complaints as angina pectoris, seasickness, anxiety and tension, or the common cold could be cured by the giving of a placebo tablet of plain lactose.

Double-blind Trials

The difficulty of knowing whether a new drug was really active in man or whether its effects were those of a placebo had led to the introduction of the "double-blind" trial. In such a trial there were, so to speak, two blind men. One was the patient, who was unaware whether a tablet was a genuine tablet or a dummy, and the other was the doctor who gave the tablet and judged its effects. The tablets were handed to the doctor by a third person who alone had the key to their composition. This method was ideal for determining the action of a new drug when its effects were sufficiently objective. This had been well illustrated in the test of streptomycin carried out on patients with tuberculosis for the Medical Research Council.

The double-blind trial could, however, be misapplied, and when it was misapplied it could give disquieting results. Thus Batterman and Grossman[1] had been very disturbed when they tested well-established analgesic substances by this method. They said, "It is with surprise that we note the same effectiveness for placebo medicaments, known effective analgesics, and unknown drugs. Regardless of the medicament administered we always achieve the same result. There appears to be an incidence of effectiveness that occurs with all medicaments with the double-blindfold technique regardless of what preparations are being investigated." They further said that placebos which were by usual methods 40% effective were by the double-blind method 60% effective. They came to the conclusion that no difference between tablets of aspirin and tablets of lactose could be detected unless at least the physician knew what he was giving.

Modell and Houde[2] had discussed these findings and had made some observations of their own. They first made tests very much in the same way as Batterman and Grossman. They studied 25 patients with arthralgic pain, and treated them with aspirin in doses of 250 mg., 500 mg., and 1,000 mg. Each of these doses was given to a patient three times a day. Each patient was also given tablets of lactose three times a day. The results as recorded by the patients at the end of two weeks had indicated no difference between aspirin and tablets of lactose. Thus, when taking tablets of lactose, 38% were improved, 38% were not affected, and 24% were worse. When taking 1 g. of aspirin, 44% were improved, 31% were unaffected, and 25% were worse. However, Modell and Houde said that the patients had not kept trustworthy records, some of them only filling up their cards when they came to the clinic at the end of two weeks, by which time they had forgotten what degree of pain relief they had had. Batterman and Grossman had obtained their results in this way. Modell and Houde then made further observations in which the patients were again given tablets, but this time the patients communicated what relief of pain they felt directly to an observer during the five-hour period after taking the tablets. In this study a clear difference was obtained, aspirin producing a much greater and more prolonged effect than lactose. Modell and Houde emphasized that the difficulties some observers had had in applying the double-blind test to substances of known efficacy could be explained by insufficient care in the collection of results and by too much reliance on the patient's memory.

Unexpected Placebo Effects

There was still another side to the giving of a placebo, for not only might it have curative effects but it might also exert side-effects or unwanted effects. It was not on reflection wholly surprising that when a patient who was suffering from pain was given a tablet in circumstances which suggested that it might relieve his pain he should feel some relief. It did, however, seem strange that he should have side-effects. Yet such symptoms were on solemn record.

A different problem created by the placebo had been demonstrated by Modell and Garrett.[3] All persons had a certain degree of finger tremor of high amplitude. This finger tremor was measured in 12 male students, and found to be at the rate of 60 per min. The tremor was increased by mental work when the students were competing with one another in performing a particular task, and the figure rose from 60 to an average of 152. Now the point of interest was that when the students were given a dummy tablet beforehand (not knowing that the tablet was a dummy), and then repeated the exercise, the finger tremor rose to an average of 198. Thus the taking of a dummy tablet had made the degree of finger tremor worse. It was clear that the taking of a tablet had created apprehension in spite of the fact that the subjects were aware that the purpose of the investigation was to test tablets for their power to allay apprehension. When, instead of a dummy tablet, a tablet containing 100 mg. phenobarbitone was taken, the finger

[1] Batterman, R. C., and Grossman, A. J., *J. Amer. med. Ass.*, 1955, **159**, 1619.
[2] Modell, W., and Houde, R. W., ibid., 1958, **167**, 2190.
[3] —— and Garrett, M., *Nature (Lond.)*, 1960, **185**, 538.

tremor rose to 162 only. Thus the phenobarbitone reduced the apprehension created by the taking of a tablet, but not so much that the result was better than no tablet at all.

New Tranquillizers

Clearly the testing of new drugs in man was not easy. As a result there must always be uncertainty whether a new drug had a useful action which was peculiar to it and not possessed by other drugs already in use. The new drugs which had been introduced during the last eight or nine years as tranquillizers were very expensive. There were doubtless large numbers of chemical compounds to be found which would tranquillize a fierce monkey or dog, and some of these when tested clinically might appear from results in the first one or two hundred cases to be freer from side-effects than their predecessors. These were the drugs which were selected for advertisement to the medical profession. As could be readily imagined, it often remained uncertain whether they had any special properties which were useful. There were two tranquillizing agents about which there was no doubt, and these, reserpine and chlorpromazine, both had actions which were sufficiently well defined to be studied in animals in many different ways. Concerning most others this was not true. For some of them effects had been discovered in animals, but these effects were not obviously useful in man.

"To me," said Professor Burn, "it seems at least a tenable view that drugs which are effective in the brain will always be found to have properties which can be observed in the rest of the body. This is true, for example, of reserpine, chlorpromazine, nicotine, and also of cocaine. Unless the manufacturer discovers a new drug which produces clearly understood peripheral and central effects in animals, I would be inclined to discourage him from selling it if his only ground for doing so is that it has a general tranquillizing action and is not obviously harmful in man."

A Twice-trodden Path

We were at the moment retreading a path which we had trodden before. Some thirty years ago the battle was being waged about the sale of medicaments which had not been tested on animals. There was "hormotone," a mixture of dried animal glands to be taken by mouth. It was devoid of activity except that due to the presence of a small amount of thyroid. There were large numbers of other preparations. But the battle was won, and it became the rule for pharmaceutical houses to subject their products to animal tests both for potency and toxicity. That was a considerable advance.

Now so far as concerned the tranquillizing drugs we were back again where we were. Having established that a new substance would tranquillize a monkey or a dog, a manufacturer relied on clinical reports. Professor Burn said he had tried to show, by examples of the effects of placebos, how misleading these clinical reports could be. The accident that French workers discovered the usefulness of chlorpromazine in patients before it was shown to exert its tranquillizing properties in animals had no doubt been responsible for this situation. But reliance on clinical reports was not enough. Clinical trials would of course be needed at the end, but better-devised tests on animals, as the result of much more extensive study of the animal brain, were required. "I am convinced," said Professor Burn, "that it is only in this way that the advances will come."

The *Charaka Sahita*, an important work on Ayurveda, Ceylon's indigenous system of medicine, has been translated into Sinhala from Sanskrit. Although there have been books on Ayurveda in Ceylon for a number of centuries, important works such as the *Charaka Sahita*, *Susrutha Sahita*, and *Voagbhate Sahita* had not so far been translated fully into Sinhala. The Department of Indigenous Medicine is therefore taking steps to have these books translated under the auspices of the Official Languages Department.

APPROVED NAMES

The last supplement to the consolidated list of "approved names" was published in the *Journal* of September 3 (p. 729). A new supplement, dated November, 1960, is printed below. Communications relating to "approved names" should be addressed to the Secretary, British Pharmacopoeia Commission, General Medical Council, 44 Hallam Street, London W.1.

Approved Name	Other Names	Notes
Amphomycin ..	An antibiotic produced by *Streptomyces canus*	Antibiotic
Betamethasone ..	9α-Fluoro-11β : 17α : 21-trihydroxy-16β-methylpregna-1 : 4-diene:3 : 20-dione 9α-Fluoro-16β-methylprednisolone	Cortico-steroid
Biperiden ..	1-(*bicyclo*[2 : 2 : 1] Hept-5-en-2-yl)-1-phenyl-3-piperidinopropan-1-ol The name "akineton" is applied to the hydrochloride and the lactate	Treatment of Parkinson's disease
Chlordantoin ..	5-(1-Ethylpentyl)-3-(trichloromethylthio)-hydantoin	Fungicide
Chlordiazepoxide	7-Chloro-2-methylamino-5-phenyl-3H-benzo-1 : 4-diazapine 4-oxide "Librium" is the hydrochloride	Treatment of neuroses and psychoses
Chlorprothixene	α-2-Chloro-9-(3-dimethylaminopropyl-idene)-thiaxanthen "Taractan"	Treatment of neuroses and psychoses
Chlorthalidone ..	3-(4-Chloro-3-sulphamoylphenyl)-3-hydroxy-*iso*indolin-1-one "Hygroton"	Oral diuretic
*Clonitazene ..	2-*p*-Chlorobenzyl-1-(2-diethylaminoethyl)-5-nitrobenzimidazole	Narcotic
Demecarium Bromide	Decamethylenebis (*m*-dimethylamino-phenyl-*N*-methylcarbamate) dimethobromide "Humorsol"	Treatment of glaucoma
Dioxamate ..	4-Carbamoyloxymethyl-2-methyl-2-nonyl-1 : 3-dioxolan	Treatment of Parkinson's disease
Ectylurea ..	α-Ethylcrotonylurea "Nostyn"	Sedative
Ethchlorvynol ..	5-Chloro-3-ethylpent-1-en-4-yn-3-ol "Placidyl"	Hypnotic
Ethosuximide ..	α-Ethyl-α-methylsuccinimide "Zarontin"	Treatment of petit mal
*Etonitazene ..	2-*p*-Ethoxybenzyl-1-(2-diethylaminoethyl)-5-nitrobenzimidazole	Narcotic
Hexapropymate	1-Propynyl*cyclo*hexyl carbamate "Merinax"	Sedative
Hydromorphinol	14-Hydroxydihydromorphine	Analgesic narcotic
Isoaminile ..	4-Dimethylamino-2-*iso*propyl-2-phenyl-valeronitrile "Dimyril" is the citrate	Antitussive
Isoxsuprine ..	1-*p*-Hydroxyphenyl-2-(1-methyl-2-phenoxyethyl-amino)-1-propanol "Dilavase" is the hydrochloride	Vasodilator
Methicillin ..	6-(2 : 6-Dimethoxybenzamido) penicillanic acid "Celbenin" is the sodium salt; "staphcillin" is the sodium salt	Antibiotic
Oxymetholone ..	2-Hydroxymethylene-17α-methyldihydrotestosterone "Anapolon"	Anabolic steroid
Pemoline ..	2-Imino-5-phenyloxazolidin-4-one "Kethamed"; "pioxol"	Central nervous system stimulant
D-Penicillamine	(–)-ββ-Dimethylcysteine	Treatment of Wilson's disease
Phenbutrazate ..	2-(3-Methyl-2-phenylmorpholino) ethyl α-phenylbutyrate	Appetite suppressant
Phendimetrazine	(+)-3 : 4-Dimethyl-2-phenylmorpholine "Plegine" is the tartrate	Appetite suppressant
*Phenoperidine	Ethyl 1-(3-hydroxy-3-phenylpropyl)-4-phenylpiperidine-4-carboxylate	Narcotic
Pipazethate ..	2-(2-Piperidinoethoxy)ethyl 10-thia-1 : 9-diaza-anthracene-9-carboxylate "Selvigon" is the hydrochloride	Antitussive
Plasminogen ..	The specific substance derived from human plasma which, when activated, has the property of lysing fibrin	
Pyrazinamide ..	Pyrazinoic acid amide	Treatment of tuberculosis
Sodium Ironedetate	Iron chelate of the monosodium salt of ethylenediamine-*NNN'N'*-tetra-acetic acid "Sytron"	Treatment of iron deficiency anaemia
Streptodornase ..	An enzyme obtained from cultures of various strains of *Streptococcus haemolyticus* and capable of catalysing the depolymerization of polymerized deoxyribonucleoproteins	
Streptokinase ..	A co-enzyme obtained from cultures of various strains of *Streptococcus haemolyticus* and capable of changing plasminogen into plasmin	
Tranylcypromine	(+) *trans*-2-Phenyl*cyclo*propylamine "Parnate" is the sulphate	Anti-depressive

* Narcotic substances which fall under International Control and are not available as therapeutic agents.

STIMULATION OF ANTIBODY PRODUCTION

[FROM A SPECIAL CORRESPONDENT]

The British Society for Immunology opened its autumn meeting on November 25 and 26 with a symposium on "Stimulation of Antibody Production." Sir JOHN BOYD, F.R.S., was in the chair. Underlying this title was the very practical problem of how immunizing agents can be made to give of their best. The problem has two main facets: that of the antigen, and that of the host. The antigen must be presented in a form and dosage and so timed that the body takes the fullest cognizance of it; on the other hand, the tissues of the host can sometimes be conditioned, by means of adjuvants, to be at their most receptive or productive. In practice these aspects are often inseparable.

Maternal Antibody and Immunological History

Considerations of dosage and timing were admirably illustrated by Dr. F. T. PERKINS, who described the difficulty of breaking through the cloak of maternal antibody in poliomyelitis vaccination of the 1-week-old infant. The need for such early immunization was an administrative one; it was easy to persuade the mother before she left hospital, but if vaccination was deferred till later there was a tendency to default. Two doses of a normal vaccine were insufficient to overcome maternal antibody. Increasing the number of doses to three led at once to considerably better titres and to better booster responses some months later. Even so, the response to type 1 virus was still unsatisfactory. The use of three doses of a concentrated vaccine with a greatly increased content of type 1 raised the type 1 antibody to satisfactory levels and further improved the responses to types 2 and 3.

The difficulty posed by the presence of maternal antibody is one example of the importance of the immunological past history. Miss MOLLIE BARR gave two further instances of the way in which previous antigenic experience can interfere with antibody responses. The first showed how an animal actively engaged in producing antibody to one antigen could almost disregard, in terms of circulating antibody, doses of another antigen to which it had previously responded well, and how this original power to respond was restored after a suitable resting period. In the second, guinea-pigs immune to T.A.B. vaccine were given two spaced doses of tetanus toxoid; if the first of the two doses was accompanied by a booster dose of T.A.B. the tetanus response was much depressed.

Combined Prophylactics

The increasing need for combined prophylactics, to confer the widest protection with the minimum number of injections, requires that we should understand as fully as possible the interactions between antigens given in mixture or in fairly rapid succession. Relevant here was Madame M. KAMINSKI'S communication on the heterogeneity of antibodies to single proteins, indicating that single proteins also might behave as multiple antigens. Madame Kaminski reviewed in some detail enzymic digestion methods whereby the multiple determinant groups of such proteins might be distinguished and analysed.

Mixing antigens may result either in interference or in enhancement of the antibody response, and the proportions in which they are mixed may also be significant. Miss BARR described how a fourfold increase in the tetanus content of a mixture could reduce the response to diphtheria with no gain to the tetanus response. Dr. F. L. ADLER discussed how, in mice, bovine gamma globulin could interfere with responses to a wide range of doses of crystalline ferritin. Transfer of mixtures of splenic cells from donor mice immunized with one or other antigen suggested that the depression was not due to competition for a common metabolic precursor. Using T_2 phage and haemocyanin in the primary antibody response of rat cells *in vitro* competition occurred only during the interaction between antigen and macrophage but not during the subsequent phase of production of antibody by lymph-node cells.

Mutual Enhancement

Mutual enhancement was treated also by Miss BARR, who described the accelerating effect of T.A.B. vaccine on responses to tetanus toxoid. The effect only occurred if the antigens were mixed and not if they were injected into widely separated sites. Dr. L. B. HOLT described the enhancing effect of pertussis vaccine on diphtheria toxoid, and showed that there was a linear relationship between the arithmetic dose of pertussis and the log. diphtheria response in children. This observation accorded well with that of Dr. J. R. FARTHING on guinea-pig responses. Dr. Farthing, however, unlike Miss Barr, found that separate but adjacent sites of injection did produce some enhancement, an effect probably attributable to common lymphatic drainage. Dr. Farthing had investigated also chemical fractions of the pertussis organism; as in other Gram-negative organisms, the active factor proved to be the lipid A moiety of the lipopolysaccharide. Dr. HOLT found no correlation between the enhancing effect and agglutinin titres to pertussis, and Dr. FARTHING found no evidence of correlation with the stress effects of endotoxin.

Adjuvant Action

Contributions to the subject of adjuvant action generally were made by Dr. HOLT, who showed differences between dose–response regression lines for fluid diphtheria toxoids and toxoids adsorbed on mineral carrier, and by Dr. R. G. WHITE, who surveyed the tissue responses of the host to alum and to water-in-oil emulsions. As shown by the fluorescent antibody technique there was both localization of antigen in the granuloma and local antibody production. But in spite of demonstrable persistence of antigen in the granuloma antibody production fell off. The addition of mycobacteria to water-in-oil emulsions increased and prolonged the antibody response, but in this case there was curiously little local antibody production. The increase was attributable to remote widespread proliferation of plasma cells.

The possibility of influencing antibody-producing cells by direct stimulation of the nucleic-acid mechanism was illustrated by the enhancing action of colchicine. Dr. White discussed this observation in relation to the action of *x* rays. Professor C. L. OAKLEY, summing up, reminded the audience that there were still omissions among the day's topics, and made a final plea that in the struggle to stimulate greater and greater quantities of antibody they should not lose sight of the factor of quality.

Nova et Vetera

REITER'S DISEASE

BY

J. K. OATES, M.B., M.R.C.P.Ed.

AND

R. M. MASON, D.M., M.R.C.P.

The London Hospital

In 1916 Lieutenant Hans Reiter[1] of the German Army Medical Corps described the case of a German lieutenant who was admitted to a field hospital on August 28 of that year, giving a history of abdominal pain and diarrhoea with a little blood, followed eight days later by a purulent urethral discharge associated with a "purulent catarrh of the conjunctivae of both eyes." A few days later he developed arthritis of both

knees, and thereafter multiple joints were affected, so that after two months he had to be transferred to the garrison hospital. On October 23 he was noted to have unilateral iritis. He evidently steadily improved, and the last recorded observation on him was on November 18, 1916. Reiter attributed this disease to a spirochaete he had isolated from blood culture, and he entitled his report, "On a hitherto unknown infection caused by a spirochaete." From that day the syndrome has borne Reiter's name.

During July to October, 1916, an epidemic of bacillary dysentery occurred among French troops on the Somme. Noel Feissinger and Edgar Leroy[2] reported four cases of polyarthritis, including involvement of the vertebral column and the instep, among the victims, and drew attention to the occurrence of urethritis and conjunctivitis in these cases. They entitled the condition "conjunctivo-urethro-synovial syndrome," but subsequent French writers have usually referred to it eponymously after these authors.

It should be noted that both these descriptions refer to patients who developed this condition after dysentery, and, in view of the fact that both reports refer to exactly the same period of time, it is tempting to speculate on the intriguing possibility that perhaps Reiter's patient was also serving on the Somme, although on the opposing side, and even on the possibility that the troops of both armies drew their water from a common source. This, however, is not the case. Reiter's patient was serving on the Balkan Front.[3]

However, in 1818, 98 years earlier, Sir Benjamin Brodie,[4] then assistant surgeon at St. George's Hospital, published his book *Pathological and Surgical Observations on Diseases of the Joints* in which he wrote: "The following case furnishes an example of a disease which, as far as I know, has not been described by any pathological or surgical writer." He described five cases in all, and the first case bears repetition as a classical example of superb clinical description, executed with a masterly economy of words.

"A gentleman, forty-five years of age, in the middle of June, 1817, became affected with symptoms resembling those of gonorrhoea. There was a purulent discharge from the urethra, with ardor urinae and chordee. On the 23rd of June he first experienced some degree of pain in his feet. On the 24th, the pain in the feet was rather increased, but not in a sufficient degree to prevent his walking four miles. There was some appearance of inflammation of his eyes.

"June 25th, the pain in his feet was more severe; the tunicae conjunctivae of his eyes were much inflamed, with a profuse discharge of pus.

"These symptoms increased in violence, the pulse varying from 80 to 90 in a minute: the tongue being furred; and the patient being restless and uncomfortable during the night. The whole of each foot being swollen; there was inflammation of the synovial membranes of the ankles; and it appeared to me, that the affection of the feet themselves arose from inflammation of the synovial membranes belonging to the joints of the tarsus, metatarsus, and toes. He said that he could compare the pain, which he experienced, to nothing else than that which might be supposed to arise from the feet being squeezed in a vice.

"On the 27th of June the left knee became painful, and on the following day the synovial membrane of this joint was found exceedingly distended with synovia. He was now completely crippled; compelled to keep his bed, and scarcely able to vary his position in the smallest degree without assistance. The inflammation of the eyes and urethra was somewhat abated.

"June 30th, the inflammation of the eyes and urethra had much subsided, and the purulent discharge was diminished. The pains of his joints were less severe; and the feet were less swollen. On the following day the knee was less swollen also.

"He continued to mend, and on the 10th of July the swelling of the feet was still further diminished, and that of the knee had almost wholly disappeared. His pulse continued to vary from 80 to 90 in a minute, and his tongue was still furred. He had pain in the feet and knee, but less severe than formerly, and he was restless at night.

"July 13th, he complained of pain in the right knee, and on the following day there was pain also of the right elbow and shoulder.

"The right knee afterwards became swollen from fluid within the cavity of the synovial membrane, but not in the same degree with the other knee, and the swelling soon subsided. There was never any perceptible swelling of the shoulder and elbow.

"August 1st, all his pains were abated. The eye and the urethra were nearly free from inflammation, and the purulent discharge was scarcely perceptible.

"August 5th, he was free from pain except on motion; the joints, which had been affected, were stiff; but he was able to move about on crutches.

"From this time he progressively mended. The stiffness of the joints diminished very slowly; but he was free from all uneasiness. He was longer in recovering the use of the shoulder than that of the other joints.

"In the following December, 1817 (at which time he had nearly, but not completely, recovered the use of his limbs), he had another attack of the complaint. The symptoms were the same as formerly, taking place in the same order, and pursuing the same course, but with a much less degree of violence. This second attack lasted about six weeks; and left him again considerably crippled.

"In March, 1818, he became affected with an ophthalmia, but of a different nature, from that which he laboured under in the preceding summer. The inflammation was seated in the proper tunicks of the eye; and it appeared probable, that it would speedily have terminated in adhesions of the iris, and destruction of the powers of vision, if its progress had not been arrested, by repeated blood-lettings, and the use of mercury.

"In order that the history of the disease might be rendered as simple as possible, I have described the symptoms in this case without hitherto adverting to the treatment, which was employed.—Leeches, and blisters to the knee; liniments rubbed on the knees and shoulders; and fomentations when there was severe pain; formed the principal topical remedies. Of the various medicines, which were exhibited, none seemed to be productive of benefit with the exception of the *vinum colchici*. It was under the use of this medicine, that not only the pains and swellings of the joints; but that even the purulent inflammation of the eyes and urethra first began to subside: and I am on the whole inclined to believe that my patient was indebted to it for a much more speedy recovery than he would have had otherwise."

Six years later, in 1824, Sir Astley Cooper[5] in his Surgical Lectures on Venereal Diseases, given at St. Thomas's Hospital, included rheumatism among the complications of gonorrhoea, and he described the following case.

"An American gentleman came to me with a gonorrhoea, and after he had told his story, I smiled, and said to him—do so and so, particularizing the treatment, and that he would soon be better; but the gentleman stopped me, and said, 'not so fast, sir; a gonorrhoea with me is not to be made so light of, it is no trifle; for in a short time you will find me with inflammation in the eyes, and in a few days after, I shall have rheumatism in the joints. I do not say this from the experience of one gonorrhoea only, but from that of two, and on each occasion I was afflicted in this manner.' I begged him to be careful to prevent any gonorrhoeal matter coming in contact with the eye, which

(*Continued at foot of next page*)

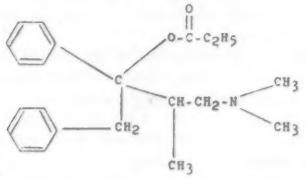
To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in current use.

Dextropropoxyphene Hydrochloride

"Doloxene" (Eli Lilly).

Chemistry. — This synthetic analgesic is chemically α-(+)-4-dimethylamino-1 : 2-diphenyl-3-methyl-2-propionyloxybutane hydrochloride, and has the following structural formula:



Therapy.—This is a relatively new mild analgesic, which has, however, been subjected to fairly extensive clinical trials. It seems to be as effective as codeine phosphate in its analgesic action, but has fewer of the undesirable side-effects of codeine, particularly its constipating action. The drug is given orally, and the usual adult dose is 65 mg. three or four times daily either alone or in combination with aspirin. It seems to have some merit and indeed may be superior as an analgesic in those conditions for which compound codeine tablets are commonly prescribed.

Side-effects.—Occasionally skin rashes and nausea have followed the administration of doloxene. So far in therapeutic tests no evidence of damage to the haemopoietic, renal, or hepatic systems has been reported, and physical dependence and tolerance have not been observed.

N.H.S. Basic Price.—Pulvules, 32 mg., 100 for 13s. 4d.; 65 mg., 100 for 25s.

(*Continued from previous page*)

he said he would. Three days after this I called on him, and he said, 'now you may observe what I told you a day or two ago is true.' He had a green shade on, and there was ophthalmia of each eye. I desired him to keep in a dark room, to take active aperients, and apply leeches to the temples, in order to reduce the inflammation. In three days more he sent for me rather earlier than usual, for a pain in one of his knees (the left), it was stiff and inflamed; I ordered some applications, and soon after the right knee became affected in a similar manner. The ophthalmia was with great difficulty cured, and the rheumatism continued many weeks afterwards. This case struck me very forcibly, and I asked Mr. Cline, with whom I was in the habit of frequently coming in contact, whether he had ever seen rheumatism proceeding from gonorrhoea? and he replied, 'Several times.'"

The descriptions of the illness detailed here extend over a period of 98 years. Each of the authors seemed to consider that the condition had not previously been characterized. Brodie's account was not only the first but the most outstanding, and from the point of view of lack of ambiguity alone it deserves to rank as the definitive description.

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Correspondence

External Cardiac Massage

SIR,—In your annotation entitled "Cardiac Massage without Thoracotomy" (November 26, p. 1582) you describe "a new method of performing cardiac massage" by a team from Johns Hopkins University.[1] Their carefully conducted experiments on dogs and their high rate of success on actual patients (14 survivals among 20) must surely impress those who advocate the use of a knife first, second, and always.

The American team refer in their article to the paper by Dr. Bullough and myself[2] which you published in 1957. Our method differs from that of Dr. Kouwenhoven and associates in several respects. We place one arm under the patient's neck, the other behind his knees, flex his knees and thighs on to his chest, exert pressure on to the chest, and then fully extend the patient before starting another "concertina." We claim that by this manœuvre we empty the leg veins of venous blood, "massage" the heart, and ventilate the lungs. Inflation of oxygen is employed during the extension phase if available. Our recovery rate among eight patients ranging from 8 weeks to 13 years was 100%. All had been anoxic before cardiac arrest supervened, none had ventricular fibrillation.

Since our paper appeared I have been able to apply the same method equally successfully on a somewhat obese adult patient. She had been anaesthetized and intubated prior to reduction of a fractured nose. The endotracheal tube was subsequently found to have been blocked by the top of a glass ampoule. By the time it was realized that failure to inflate her lungs was due neither to bronchial spasm nor to the anaesthetist's ineptitude, her heart suddenly stopped beating. The endotracheal tube was pulled out and a knife sent for. While waiting for this, I started resuscitation by the combined leg-flexion, chest-compression manœuvre described. Within half a minute—the time it took to fetch a knife from the theatre—the pulse had returned and respirations began soon after. The patient was then reintubated with a patent tube, the fracture reduced, and she suffered no ill-effects. A similar[7] method to ours was used by Stout[3] on a man who suffered cardiac arrest after sternal puncture. His account is well worth reading both for its graphic description and for its theorizing on the mechanism involved. I should also draw attention to Woodward's recent paper on "Cardiac Arrest Treated by Elevation of the Limbs for 15 Secs."[4] Many authors have shown that a circulation can be maintained after the heart has stopped.[5–7]

The appalling tragedy which cardiac arrest constitutes makes it imperative that a programme of careful animal experimentation be instituted in this country in order to evaluate the different methods of resuscitation (closed as well as open chest). Dr. Bullough and I had hoped to do some animal experiments, but were hampered by lack of suitable facilities.—I am, etc.,

Chislehurst, Kent. E. H. RAINER.

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Salary Crisis at Cambridge

SIR,—It is astonishing that none of your correspondents on this subject has mentioned what is for the future its most important aspect.

Dr. D. H. M. Woollam's account (December 10, p. 1731) of medical education at Cambridge is incomplete. It is true that medical students leave here after their preclinical training, which is carried out mainly by the fundamental science departments, and return only to sit for their final examinations. What he omits entirely is that last year the University decided on a major extension of its *postgraduate* medical work.

In a report of the Council of the Senate on developments of the Medical School, dated May 25, 1959, it was stated that "after careful consideration of all the factors the Council have come to the conclusion that the proper course for the University is to concentrate its resources on the development of the thriving postgraduate Medical School. . . . The Board of Governors (of the Hospitals) have informed the Vice-Chancellor that they are entirely happy with the Council's decision." The Council of the Senate recommended that "general approval be given to the policy outlined in this report for the development of the School of Clinical Research and Post-Graduate Teaching." This will be housed on the new site on which the United Cambridge Hospitals are being completely rebuilt. Its work will be closely associated with that of the hospitals as well as with that of the strong departments already existing in the University in the sciences basic to medicine. In fact, a unique opportunity has been seized to develop in Cambridge a special, and very badly needed, type of postgraduate medical school, as was recommended in the Goodenough Report. It is this that is in danger of being thrown away if the salary proposals of the University Grants Committee are rejected.

Personnel of the highest quality is essential for the success of this new development. Undoubtedly working in Cambridge has its great attractions on any income. But it is no reflection on possible candidates to say that in spite of this many of the best will feel bound to go elsewhere if offered higher salaries for the work they want to do.—I am, etc.,

Addenbrooke's Hospital, Cambridge. H. R. YOUNGMAN.

SIR,—Correspondence resulting from your leading article entitled "Salary Crisis at Cambridge" (November 26, p. 1579) has raised the question of the differential between medically qualified staff of clinical and preclinical departments. Here I fully support the view expressed by Dr. E. H. L. Harries (December 10, p. 1730) that the policies of the B.M.A. and of the universities are not irreconcilable.

The Belfast scheme whereby medically qualified people in preclinical departments are employed jointly by the university and by the Health Service has, I understand, worked well. To-day there are probably few doctors in preclinical departments whose work does not overlap with that of their clinical colleagues. Several make a direct contribution to the Health Service, other than by teaching, by performing special tests and investigations. I believe that the rigid subdivision into "clinical" and "preclinical" disciplines is passing as biochemical and physiological principles enter more and more into diagnosis and treatment. Clinical and preclinical staff are increasingly working together both in teaching and in research.

Whether or not university salaries, both clinical and non-clinical, are nevertheless adequate for a comfortable existence (Mr. Edward Grant, December 10, p. 1731) here seems immaterial. The tragedy of the differential between medically qualified members of university clinical and preclinical departments is that it perpetuates a rigid subdivision at a time when workers in both fields are trying to bring them closer together.—I am, etc.,

Hersham, Surrey. M. J. ALLWOOD.

Radiological Hazards to Patients

SIR,—The general recommendations (December 10, p. 1727) of Lord Adrian's Committee, if acted upon, will go a long way towards reducing radiation dosage, but I would have welcomed one more recommendation which would have condemned, or at least discouraged, the existing practice by which general practitioners can refer their patients direct to the radiologist, bypassing the out-patient department of the hospital and thus depriving the clinician of the chance of expressing his opinion. I have no doubt, from innumerable experiences, that had the clinician's opinion been sought in these cases the number of *x*-ray examinations could have been considerably reduced. I quote only two recent examples to illustrate my point:

A female patient was referred, following a haemoptysis, direct to the radiologist of a hospital. Between April 27 and May 5, 10 full-size films were taken of her chest, and in addition she was submitted to 10 more exposures for tomograms. Thus, she had 18 exposures without arriving at a diagnosis. Had this patient been referred to the clinician in the first instance, he would have made the correct diagnosis of respiratory tuberculosis on taking the history, clinical examination, a single *x*-ray film, and one sputum examination. The other case was of a man, again following haemoptysis, who had six full-size films (postero-anterior, right lateral, left lateral, right anterior oblique, right posterior oblique, transverse for presentation of the diaphragm), while a clinician would have needed only a maximum of two films (postero-anterior and right lateral) to come to the conclusion that further radiology could not be of any possible help in establishing the diagnosis and that immediate bronchoscopy was essential.

It must be obvious from these two examples that the radiologist, when asked by the general practitioner to act as a direct consultant, feels that he *must* make the diagnosis, disregarding completely the limitations of the technique and thus increasing without any benefit to anyone the radiological hazards. Radiology can never be more than one of the ancillary methods of diagnosis, and unless its use is left in the hands of the clinician, who can *co-ordinate* it with other diagnostic methods, it will always be a potential danger to the patient.

I feel that as this is not a local, but nation-wide, problem, to avoid unnecessary embarrassment to the radiologists who could easily be identified from my name and address, I should, at least for the time being, remain

ANONYMOUS.

Shortage of Radiographers

SIR,—Your report that the shortage of radiographers caused less than a 24-hour casualty service at the Birmingham Accident Hospital (September 17, p. 875) makes me ask why doctors do not take their own films. The cases where delay occurred were minor injuries. Why not equip two rooms in casualty, one with a small

tube above a couch (for example, a Watson MX2 unit) and the other as a dark room? Then let the doctor on duty decide within 20 minutes if, for instance, his patient has only a severe sprain or a fracture. I am able to do this with no more training than that received as an undergraduate together with a few hours with a technician. It is ludicrous to think that in an African bush hospital with 75 beds and one doctor we can apparently give better service for minor injuries than you can get in Birmingham.—I am, etc.,

J. E. PARRY.

Mbereshi Mission Hospital,
N. Rhodesia.

Smallpox in Nyasaland

SIR,—Instructed by a meeting of members of the Nyasaland Branch of the B.M.A., I am to request you to publish the following statement:

In November of this year the Director of Medical Services, Nyasaland, made public the incidence of smallpox over the last few months, together with the areas involved and the number of fatal cases. Subsequently a member of the Association denied the existence of the outbreak in a statement made by him to the Press in London.

The Nyasaland Branch of the B.M.A. is satisfied that the figures on the incidence and mortality as published by the D.M.S. are correct and based on infectious diseases notifications rendered by members of the profession in this country. Furthermore, several members of the Association with many years of service to the local population expressed their considered opinion that for every notified case of infectious disease there are several undetected and therefore not notified cases.

The Nyasaland Branch, like all other Branches of the B.M.A., is a non-political, professional body open to doctors of any race or political belief.

The above statement is published to make known the true facts.—I am, etc.,

HENRY MOWSCHENSON,
Honorary Secretary,
Nyasaland Branch, B.M.A.

Blantyre.

Service Overseas

SIR,—Having recently spent two years in Uganda, I have read your recent correspondence on this subject with great interest. Though agreeing with Mr. David Patey (December 3, p. 1668) that secondment arrangements can make only a minor contribution to the development of medical services in developing countries, I think that they are of special value for the following two reasons:

(1) Seconded officers know that they have only a limited time—usually two years—in which to accomplish a particular job or to make some impression in the developing health service of the country they are working in. They therefore are likely to get down to work with zeal which is unlikely to be maintained for more than a limited period.

(2) Specialists who have spent some time on secondment are also in a specially favourable position to help postgraduate students who have come to this country for higher degrees. Very often they will be only too pleased to introduce them in the hospitals to which they are attached here, either with a view of obtaining suitable resident appointments or only to enable them to get an idea of English hospital life when they are here for non-clinical courses. Having found that one Uganda student for the primary F.R.C.S. had never seen the inside of an English hospital during almost a year's stay in this country, the Hospital of St. Cross, Rugby, has offered admission as postgraduate students for short periods to all Uganda graduates, hoping to make their studies here easier and helping the friendly feelings between these countries. I hope that similar arrangements will in time be made with other hospitals who have on their staff specialists who have worked on secondment.—I am, etc.,

P. E. ROLAND.

Rugby.

White Mouse Medicine

SIR,—The letter from my friend Dr. Richard Mackarness (December 10, p. 1737) prompts me to add to the correspondence on this topic; because it is he who for the first time raises what in my view is the crux of the whole matter. In May of this year *Family Doctor* contained an article by myself. The essence of it was that coronary heart disease was increasingly common; that, while many named factors were probably involved, it seemed likely that the quality of dietary fat was the chief; and that, accordingly, coronary patients and perhaps certain coronary "candidates" would be well advised to alter their diets. This theme seeemed to me unexceptionable, and was certainly in accord with the advice being given by many doctors in this country, and by various reputable medical journals. In October of this year—and without any notice to me—*Family Doctor* contained an article by Sir Heneage Ogilvie. The essence of it was that my views were nonsense; that my judgment and the judgment of those clinicians and research workers with whom I was in broad agreement were grossly defective; that the views in question were part of a "commercial racket"; and that the sole cause of coronary thrombosis was lack of exercise.

When I read this article, I was surprised by Sir Heneage's intemperate and quite unscientific approach, and by his gross misquotation of my own article; but what concerned me most was that he should write, and Dr. Harvey Flack, the editor of *Family Doctor*, should see fit to publish, an article that, following on my own, could arouse only doubt, and even distress, in the minds of patients and their relatives. I utterly deplore this. I was taught as a student never to criticize the decisions and opinions of a colleague in front of a patient; and I think it is a rule that helps both patients and doctors, and one to which there should be hardly any exceptions. If Dr. Flack felt the subject-matter of my article was so controversial that the official B.M.A. publication for the lay public could not properly deal with it, then he should not have published the article; and I would have accepted his decision. Having seen fit to publish it, he should certainly not, in my view, have published Sir Heneage's violent attack upon it.

I am told that my own article received various mentions in the lay press; but that Sir Heneage's received at least as many; and I do not doubt that it is the tendentious aspects of his article that have lingered in the minds of most readers. Sir Heneage has expressed regret in your columns (November 26, p. 1596) for his use of the phrase "commercial racket"; but none for anything else he said, and none at all, to my knowledge, in *Family Doctor* or in the lay press. Many ordinary people must be left with the impression that their family doctors, myself, and those consultants and research workers who favour the dietary-fat hypothesis are at best incompetents, and at worst rogues. *En passant*, Sir Heneage

Ogilvie's strong views about the "commercial racket" involved did not prevent an advertisement for an unsaturated-fat product appearing in the October issue of the medical journal of which he is editor (or, for that matter, various articles in previous issues that were in agreement with my own); nor did Dr. Flack's publication of the phrase in the October *Family Doctor* prevent him accepting revenue for advertisements in that same October issue from firms making such products. Your readers, given this summary, may now understand why I profoundly disagree with Dr. Mackarness's view that it was proper of Dr. Flack to publish both my own article and Sir Heneage's. They may also understand why I have felt a distaste for taking any part in this correspondence.

The scientific rights or wrongs of the matter are, in my view, very much less important at this moment than the ethical aspect. However, as Dr. Mackarness describes me as a "convert" to Dr. Sinclair's views, may I say that Dr. Sinclair and myself differ in this matter on a number of points?—as I am sure Dr. Sinclair would confirm. I have in fact sat at other nutritional feet than his. I have even seen Dr. Mackarness's own not irrelevant book *Eat Fat and Grow Slim*; but I certainly did not therefore feel he could properly be described as a Kekwickian. *Pace* Dr. Mackarness, both Dr. Sinclair and I think lack of exercise *is* of importance in the causation of coronary heart disease: we have both said so in print. Where we differ from Sir Heneage is in not thinking it the only factor involved. The most cursory study of the facts shows that it is not.

There are few enough facts available in this field; but at least let us be clear about such facts as are available, whether they affect the ethical or the scientific issue. And let us debate them among ourselves objectively and with mutual respect.—I am, etc.,

Amersham, Bucks. S. BRADSHAW.

SIR,—Of course I accept Sir Heneage Ogilvie's apology (December 3, p. 1674), but I cannot agree with his explanation. I criticized his erroneous statement in *Family Doctor* of October that "the Americans get more coronaries than any race in the world. They also eat far less butter than any other, and never use their muscles if they can help it"; I pointed out that the latest available figures, for 1957, showed that the mortality rate was higher for Scotland than for the U.S.A., and that obviously certain races, such as true Eskimos and some Indian races, eat less butter. Sir Heneage, in reply, quotes some selected figures for 1956 for mortality rate and butter consumption, and concludes that "America leads the field easily in coronary disease." If I may extend the figures for 1957 I quoted in my earlier letter from the latest W.H.O. source,[1] we find that in 1956 also Scotland was easily ahead of the U.S.A. in mortality rate from arteriosclerotic and degenerative heart disease (B 26) per 100,000 of population:

	1956	1957
U.S., all races	293.3	302.4
U.S., white only	306.7	316.1
England and Wales	313.3	301.3
Scotland	358.4	346.4

This, according to Sir Heneage's explanation of "simple lack of exercise," implies that the inhabitants of Scotland (diluted by a few Sassenachs who may lower the true incidence in the race of Scots) are even more sparing in the use of their muscles than are Americans.

Sir Heneage appears not to understand the basis of the hypothesis that a relative deficiency of essential fatty acids is the primary cause of coronary heart disease, since he is reported to have said (*The People*, December 4): "These cranks with the animal fat theory are even suggesting now that milk is dangerous. Next they will tell us that breast-feeding of infants is dangerous too, and that mothers should produce not milk but cod-liver oil." Human milk is much richer in essential fatty acids than is cow's milk, and is demonstrably superior for the growth of infants; but this superiority is lost when the fat of cow's milk is replaced by corn oil and two vitamins; in other words, the deficiency in essential fatty acids of cow's milk as compared with human milk is abolished by the linoleic acid in corn oil. Hartroft and his colleagues,[2] having shown that myocardial infarction could be produced in rats—white rats—when butter was included in the diet but not if corn oil was substituted for butter, compared the incidences at necropsy of myocardial infarction in patients with peptic ulcers in the U.S.A. and in England who had been treated with the Sippy diet and those who had not. In both countries the incidences were more than double in the patients treated with the Sippy diet.

Why should one suppose that peptic ulcer patients who are treated with the Sippy diet take less exercise than those not so treated? If "simple lack of exercise" is the explanation, how does Sir Heneage explain the very greatly lowered incidence of deaths from thromboembolic episodes in Torben Geill's old people given corn and soyabean oils in place of butter, lard, and margarine which I quoted in my earlier letter (November 19, p. 1520)? Sir Heneage might note the conclusion of Spain and Bradless[3] that coronary atherosclerosis is not significantly different in sedentary and physically active men dying from accidents.

Dr. Richard Mackarness (December 10, p. 1738) has misrepresented Dr. John Bradshaw, Dr. Paul White, and myself. Dr. Bradshaw (*Family Doctor*, May, 1960) wrote a well-balanced article for the lay reader on the cause of coronary thrombosis in which he correctly believed "obesity also is important, and so is lack of exercise." Sir Heneage (*Family Doctor*, October, 1960) attacked Dr. Bradshaw's article unfairly in that the statements he attributed within quotation marks to Dr. Bradshaw did not appear in Bradshaw's article; he got facts wrong as I have already pointed out; and he concluded that "the cause of coronary disease [in his opinion] . . . is simple lack of exercise." The public is not given "a balanced view of difficult medical questions" by publishing wrong facts in *Family Doctor*.

Dr. Mackarness is correct in stating that at the Conference on the Health of Executives on November 24 Dr. Paul White concentrated more on lack of exercise than on dietary fat; having had the opportunity of discussing the conference with Dr. White in the U.S. and here, I concentrated more on diet than lack of exercise, stating as follows: "I have said diet is the *primary* factor. There are other, secondary, factors that can enhance the effect of diet. *Exercise* is one, and we shall hear about this later from Dr. Paul White. . . . But, as in the example of Finland I have mentioned, lack of exercise is not the outstanding factor, and might act through diet, since if we eat the wrong fats blood clots more easily and this increased clotting is abolished by exercise." I also discussed overweight, smoking, stress, and heredity. Dr. H. Beric Wright, who was

present and whose letter you published (December 3, p. 1674), appears to have missed this. Dr. Paul White in a subsequent T.V. Panorama programme advised limitation of fats, "particularly animal fats." In this programme I did not "advocate a diet of brown bread, whisky, and cod" as Dr. R. W. Cockshut maintains (December 10, p. 1738), so the rest of his letter is irrelevant.

At the Festival Hall I made a plea for more research, particularly a large-scale trial of altered dietary fats. But we do not necessarily have to wait until proof is obtained and we understand the full details of the production and prevention of coronary heart disease: doctors rightly use aspirin to relieve headache without knowing the causes of headache, how aspirin relieves it, or even whether there is rigid scientific proof that aspirin does relieve it. The prudent man who has a family history of coronary heart disease, or has suffered from it, is, I believe, likely to modify his diet rather than put his faith solely in avoidance of "simple lack of exercise."—I am, etc.,

Oxford. HUGH SINCLAIR.

REFERENCES

1 *Epidem. vital Statist. Rep.*, 1960, **13**, 12.
2 Briggs, R. D., Rubenberg, M. L., O'Neal, R. M., Thomas, W. A., and Hartroft, W. S., *Circulation*, 1960, **21**, 538.
3 Spain, D. M., and Bradless, V. A., ibid., 1960, **22**, 239.

Control of Urinary Infections

SIR,—Your leading article (December 3, p. 1658) on urinary infection associated with catheterization is timely. Staphylococcal wound infections have until recently received the lion's share of publicity, but these iatrogenic urinary infections are probably equally common, and are the cause of much morbidity.

You fail, however, to draw attention to the question of infection ascending to the potential space between the catheter and the lining of the urethra. By scrupulous aseptic technique, and underwater drainage into formalin solution, it is possible to prevent organisms from ascending the lumen of the catheter, or being carried upwards on the point of the instrument. When drainage by indwelling catheter is maintained for any length of time, in spite of these precautions, the urine culture becomes positive, and there is much evidence that in many cases the infection has reached the bladder by ascending between catheter and urethral mucosa.

The presence of a catheter in the urethra sets up a urethritis, at first sterile due to mechanical and chemical trauma, but eventually infected by the teeming organisms of the skin of the genitalia. The barrier of the external sphincter is breached by the passage through it of the catheter, and the urethritis is followed by a cystitis. The severity of this urethritis may be reduced by employing a catheter of minimal calibre and of a bland chemical constitution (red rubber, of course, is somewhat irritating to the urethra). What is needed is a fine plastic catheter, self-retaining with an inflatable balloon, but this is apparently, as yet, beyond the ingenuity of the manufacturers.—I am, etc.,

Royal Victoria Hospital, Bournemouth. W. G. Q. MILLS.

SIR,—I was delighted to read your leading article (December 3, p. 1658) on the dangers of catheterization. In my opinion this should never be performed unless it is absolutely necessary, for even antibiotic therapy is not always successful in eradicating any acquired infection. Nor would an antibiotic umbrella be desirable or perhaps always effective.

There is, however, one forgotten drug which could safely be given in most cases, one that my father used always to use with satisfactory results in the days when asepsis was almost unknown, and that is boric acid. Though usually considered to be a very weak antiseptic, it is unexpectedly successful in most urinary infections. It makes the urine strongly acid and clears it of frank pus quite dramatically. For example, I recently had a case of enlarged prostate who, after catheterization in hospital, developed such a raging cystitis that I had to send him back three times with complete retention owing, it proved, to the urethra being blocked by plugs of pus. Eventually this infection was found to be resistant to all antibiotics, so I started him on boric acid, with immediate improvement. This kept him in comfort for nearly a year, till finally over half his bladder was removed to allow the overdistended organ to get rid of the residual urine which was keeping up the infection.

Boric acid, in doses of 10 to 15 gr. (0.65 to 1 g.) (about a tablespoonful of saturated solution at room temperature), if well diluted with water can usually be given three or four times a day for quite long periods without causing gastric irritation or the many toxic effects listed in *Martindale's Extra Pharmacopoeia*, particularly if it is combined with a carminative such as compound tincture of cardamom, but for catherization a dose before and one or two after it should suffice to prevent any infection—a simple and useful safeguard unless, of course, the investigation required makes this impossible.—I am etc.,

Winsford, Cheshire. W. N. LEAK.

Alpha-chymotrypsin in Cataract Surgery

SIR,—I should like to congratulate Mr. Dermot Pierse and Mr. H. N. O'Donoghue on their timely paper, "Alpha-chymotrypsin in Cataract Surgery" (December 3, p. 1629), which sheds much helpful light on complications alleged to be due to this enzyme. Having used this enzyme myself in over 200 cases, I am inclined to agree with their conclusion that "there were no operative complications . . . that could be attributed to alpha-chymotrypsin." The only reservation I feel is that there have been three cases of aphakic retinal detachment in my own series, which all occurred within a few months of uncomplicated intraocular extraction in which the enzyme had been used. This might only be a coincidence, or it might in fact be that the enzyme partially digests and weakens the insertion of the retina at the ora serrata during the brief time it is present in the posterior chamber. Mr. Pierse and Mr. O'Donoghue do not mention this complication, from which one deduces that they have not encountered it, but it would be interesting to know if other surgeons have met with it. Presumably several more years must elapse before there can be reliable statistical data on the late onset of aphakic retinal detachment.

I find the enzyme very helpful (1) in hypermature, swollen, or intumescent lenses at any age; (2) in patients with tough zonules between the ages of 20 and 50 years. I agree with Duthie[1] that it is desirable for the enzyme to be used on only one eye of a bilateral case of cataract extraction, so that with the passage of time a number of cases will become available for study in which the other eye in which the enzyme was not used acts as a control. I also feel that trainee ophthalmic surgeons

should not use the enzyme until they have familiarized themselves with the classical operations for cataract extraction.—I am, etc.,

Westcliff-on-Sea, Essex. D. P. CHOYCE.

REFERENCE

1 Duthie, O. M., *Trans. ophthal. Soc. U.K.*, 1960. In press.

Drinking Drivers

SIR,—I have read with interest Dr. Simon Freeman's article, "The Drinking Driver" (November 19, p. 1513), and the subsequent correspondence relating to nystagmus. Dr. Freeman's report of the presence of nystagmus in 67 out of 69 certified cases does not vary very much from my own clinical experience. In my reported series of 40 cases of suspected alcoholics in 1952[1] I found nystagmus or nystagmoid movement in 29 of them. In the series, however, was one man who had taken no alcohol and three others who had been exposed to other factors in addition to alcohol. At that time I regarded nystagmus as being associated with dilatation of the pupil with absent or sluggish reaction to light.

Subsequent laboratory investigation that I carried out in University College London and reported in 1956[2] revealed that nystagmus was the earliest eye sign produced by alcohol. It appeared before any pupil signs and was always associated with an increase in the reaction time. In that series of experiments nystagmus appeared from 10 to 60 minutes after taking alcohol, and the majority of subjects required from 0.7 to 1 ml. alcohol per kg. body-weight to produce the sign. On rough calculation, assuming beer to contain 14.7 g. alcohol per pint (0.6 litres), 2¼ to 4 pints (1.5–2.3 litres) of beer or ale should produce nystagmus in most 70 kg. men. It is surprising that Dr. John Hughes (December 10, p. 1735) did not find nystagmus in any of his subjects who had taken 4½ pints (2.6 litres) of beer, but this may have been due to the fact that they were large men or that the observation was not carried on for as long as an hour.

The absence of nystagmus in persons suffering from alcoholic intoxication may be due to the temporary high levels described by Goldberg,[3] but in addition there is a possibility that it may be absent in long-standing alcoholics as a result of damage to the nystagmus-producing mechanism which Bender and Brown[4] demonstrated when they failed with chronic alcoholics to get the normal nystagmus response to intravenous amylobarbitone sodium.—I am, etc.,

London N.W.10. DENYS E. HOWELLS.

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Howells, D. E., *Brit. med. J.*, 1952, **2**, 862.
—— ibid., 1956, **1**, 1405.
Goldberg, L., *Proceedings of First International Conference on Alcohol and Traffic*, 1951. Kugelbergs Boktryckeri, Stockholm.
4 Bender, M. B., and Brown, C. A., *Amer. J. Ophthal.*, 1948, **31**, 825.

Non-smoking Wards

SIR,—I regret that the petition recently submitted to the Minister of Health requesting side wards for patients wishing to have their treatment in wards free from tobacco air-pollution has been unsuccessful. In his reply he states: "In making rules about smoking in wards, hospital authorities will be guided by advice which they receive from their medical staffs." (See *Journal*, December 17, p. 1813.)

The report of the Central Health Services Council on the Reception and Welfare of In-patients in Hospitals, which was sent to all hospital authorities in 1953, contained the following: "In some hospitals smoking is forbidden. We think patients should be permitted to smoke at any rate during some part of the day, except where it would harm themselves or their fellows." These regulations are obviously out of date and need urgent revision.

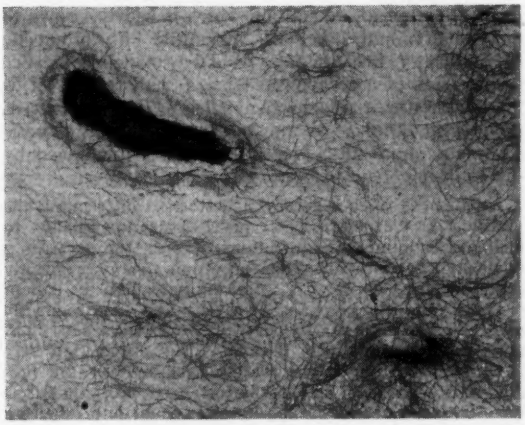
It is useless to expect any satisfactory advice from medical superintendents or consultants who have never suffered from emphysematous bronchitis, because the majority of them have not the slightest conception or personal experience of the respiratory distress caused by tobacco smoke. The only thing left for these unfortunate patients is to demand a smoke-free side ward and continue to complain to the staff and fellow patients until their request is granted.

I am surprised that the Ministry of Health has not seized this excellent opportunity of curbing the ever-increasing smoking evil. Patients should be told on admission that tobacco smoke is injurious to their own and other people's health, and that smoking is strictly forbidden. There is no doubt that this reform will come eventually, although it may take 40 to 50 years to bring British hospitals up to Continental standards, where smoking is not allowed.—I am, etc.,

Leeds 8. DAVID A. HERD.

Occupational Burn

SIR,—The combination of the conscientious alcohol-drinker and tobacco-smoker led to the unique lesion shown in the photograph. The burn resembled the trace left on piano-lids and widow-sills by departed guests,



and was produced by the simple act of leaving a glowing cigarette on the abdominal wall before going to sleep.

The burn was excised and the wound closed by suture which led to primary prompt healing. The patient has so far not done it again.—I am, etc.,

London W.1. A. DICKSON WRIGHT.

Anaemia in West Indian Infants

SIR,—The article on iron-deficiency anaemia in European and West Indian infants in London by Drs. L. R. Davis, R. H. Marten, and I. Sarkany (November 12, p. 1426) was of particular interest to me by reason of their finding that infants of West Indian racial origin, although living in urban conditions in London, had lower haemoglobin values than European infants of the same age, weight, and birth weight.

I found in Assam[1] that Indian children of the labouring class had low haemoglobin values whereas those of the middle class had similar values to European children. Moreover, this comparative deficiency of haemoglobin in labouring-class children appeared to be congenital in that seven babies followed from one to eight weeks after birth had mean haemoglobin values of only about 65% of Fitz-Hugh's normal range. The subjects of my investigation, however, were living in rural conditions, and further investigation of adult labouring-class recruits coming from rural localities elsewhere in India demonstrated that they, also, were deficient in haemoglobin. These findings, though largely in agreement with the findings of other workers so far as labourers in rural conditions were concerned, were in contradistinction to those of other workers who found no difference between Indian labourers living in urban conditions, Indian middle-class individuals, and Europeans.

It would be interesting to know whether the parents of those children studied by Davis *et al.* also had low haemoglobin values and whether they had lived in rural areas before coming to this country. Otherwise it is difficult to see why city-living West Indians should be different from city-living Indians.—I am, etc.,

Kingston-upon-Thames, Surrey. KEMPTON HARE.

REFERENCE

[1] Hare, K. P., *Ind. J. med. Res.*, 1940, **27**, 1041.

Post-anaesthetic Syndrome

SIR,—May I, through your widely read letter columns, draw attention to a condition which is widely known to anaesthetists but, I believe, very little known outside the specialty? Because of its wide diagnostic significance and its lack of a recognized label, I shall refer to it as "post-anaesthetic pseudo-meningism." The condition is at present known to most anaesthetists as "post-suxamethonium muscle-pains" and is characterized by the following type of history.

A patient is given a general anaesthetic which entails the use of a "depolarizing" muscle-relaxant—usually to facilitate endotracheal intubation—in order to perform a relatively non-incapacitating operation, very frequently dental in type. On the day following operation, the patient presents no symptoms whatsoever, and is frequently discharged from hospital. One, two, or even three days later, muscle stiffness and pain develop; their distribution may be generalized, but frequently the neck muscles are predominantly affected; the discomfort may be mild, but is quite frequently of such intensity as to simulate meningism.

The whole picture may be further confused by a mild pyrexia, which may possibly be associated with the low-grade tracheitis which sometimes follows endotracheal intubation, particularly by the nasal route. Moreover, the abdominal muscles may become sufficiently sore to interfere seriously with normal coughing; thus there is some risk of a "post-operative chest" developing.

If the patient presents this picture to his general practitioner rather than the anaesthetist—as well he might—I can imagine the very real diagnostic difficulty that might be occasioned. In conclusion, Sir, I would like to say that I write not only as an anaesthetist but as a past sufferer, and I can assure you that to anybody, such as myself, with a low pain-threshold, the condition is an extremely unpleasant and worrying one.—I am, etc.,

Dartford, Kent. MICHAEL P. COPLANS.

Dysphagia Lusoria

SIR,—I was interested to read Dr. Roy Morris's account of a patient with dysphagia lusoria (November 26, p. 1558). I was able to study a patient with the same syndrome in 1953. He was admitted to the Radcliffe Infirmary with a six-months history of dysphagia, a swelling of the neck for six weeks, and a sudden exacerbation accompanied by dyspnoea and choking. In his case, unfortunately, the swelling was seen to be due to extravasated blood and a ruptured aneurysm was diagnosed.

After an initial improvement in symptoms he died five days later. The post-mortem examination revealed the aberrant right subclavian artery. This passed behind the oesophagus where there was an atheromatous aneurysm which had ruptured into the posterior mediastinum. The patient had probably been symptom-free until six months before his death at the age of 70. This may well have been the time when his atheromatous aneurysm was developing. I think it would be a mistake to dismiss the importance of this as a possible cause of dysphagia lusoria in older patients.—I am, etc.,

The Churchill Hospital, Headington, Oxford. A. H. W. NIAS.

Preventive Medicine

SIR,—It is high time that more of us, like Dr. Anthony Eustace (November 19, p. 1524), emphasized the importance of preventive medicine. But let us be quite clear what we mean by the phrase. We do not mean merely early diagnosis. Preventive medicine aims to prevent disease ever occurring in the first place, not just to diagnose it as early as possible, important though this be in the realm of curative medicine. To aim at early detection in order to start treatment before it is too late is an admirable idea. But it is still curative medicine.

If we doctors are guilty of muddled thinking in such fundamental matters, is it any wonder the lay public are hopelessly confused by ignorance, fear, and prejudice in nearly all matters about health? The truth is that we are getting so bewildered by the astonishing advances of modern curative medicine that we are forgetting that the acquisition and retention of good health (what I prefer to call positive health) is very much a matter of common sense.

Of course a great deal of the enormous amount spent on the Health Service, as quoted by Dr. Eustace, is quite ridiculous and wasteful, aiming as it does at patching up patients who are already diseased largely through their own ignorance and laziness. How much better if a fraction of that sum were spent on preventing them from becoming diseased in the first place!

The idea of the Health Centre is an admirable one and I hope that eventually it will be the hub of the N.H.S. But let it also work in close co-operation with the Recreation Centre, the Sports Centre, gymnasiums, swimming pools, and so on. And in close association with schools and all youth organizations. Only in this way can we make it clear that physical fitness alone is the key to good health.

What is the use of spending public money on expensive slimming drugs for those who are too lazy to keep their weight down with proper dieting? If the bronchitic persists in smoking he has only got himself to blame if he gets worse. But it is our duty to convince the public of the truth of these matters. And we can only do this by a determined campaign to disseminate such knowledge by every means at our disposal. Yearly medical examination for all may be a good idea. But we must be cautious. A great deal of

imaginary disease and worry is iatrogenic and too many examinations may do as much harm as good if they are not combined with attempts at health education.

Let us be honest with ourselves. How many disease processes once started can really be cured? Patched up perhaps—but cured? Pitifully few. How many on the other hand could be prevented by healthy living! If we have consciences the answer to that is obvious. We neglect preventive medicine at our peril and the peril of our patients.—I am, etc.,

Merioneth. CLAUD C. M. WATSON.

Periodical Medical Examinations

SIR,—In view of the recent comments in your correspondence columns on the value of periodic medical examinations of apparently healthy persons, I thought that the following remarks would be in order.

In a periodic health review, it is necessary for the examining physician to have the ability and the time to make a complete examination that should include a careful history, a full clinical examination, and essential investigations such as a chest *x*-ray, urine analysis, haemoglobin or haematocrit estimation, and a cervical smear for cytologic study. I believe that other tests (for example, E.C.G., sigmoidoscopy, blood sugar) should be arranged only when they are definitely indicated. Any physician who considers that periodic examination is dull and unrewarding is doing a great disservice to his patient: in some instances, it requires greater skill to recognize a lesion in its early stage of development than it does to diagnose the same condition later.

Critics often state that the "yield" of these investigations is insufficient to justify the energy, time, and money that is required. It is obvious that the results are going to depend upon the age, sex, and social and economic levels of the patient as well as upon the effectiveness of the examination. From my experience, the lesions most frequently detected are malnutrition, hypertension and arteriosclerotic heart disease, neuroses, anaemias, renal calculi, arthritis, prostatic hypertrophy, uterine myomata, cervical erosions, breast conditions, haemorrhoids, peptic ulcers, diabetes mellitus, and goitres. It should also be remembered that these examinations may motivate persons to obtain treatment of known but neglected lesions when they did not understand what could or should be done. Health counselling is a vital part of the periodic examination, for each patient is given, in a very personal way, an accurate appraisal of his health.

Of equal importance to the initial examination is the need for careful follow-up. Naturally, an individual must be considered sufficiently responsible to follow most of the advice that he has been given, but it is also the physician's duty to ensure that any recommendations he has made are carried out in reasonable time. Furthermore, a patient should be carefully instructed to report any new symptoms that might develop and not to wait until the date of his next examination, which should depend upon his age and the state of his health. The manner in which this part of the examination is handled by the physician should depend upon the latter's impression of his patient's personality, for it is obvious that, under some conditions, hypochondriasis could be encouraged.

Granted that the obviously sick have greater need of quick medical attention, I would suggest that a physician's main duty is to prevent disease. This is the aim of periodic medical examinations.—I am, etc.,

United Nations,
New York. MICHAEL H. K. IRWIN.

Value of the Specialist's Report

SIR,—The most interesting critical analysis on this subject by Drs. R. de Alarcon, H. de Glanville, and J. M. Hodson (December 3, p. 1663) will no doubt be read by those consultants who endeavour to help us family doctors to the best of their ability. The ideals they mention would be much appreciated, but in order to obtain them such problems as clerical assistance need to be solved.

As complementary to the above, I wonder whether a small team of consultants could be persuaded to write an article on "The Value of the Family Doctor's Letter." I am sure this would be most revealing. The letters could be classified under such headings as, "Headed Notepaper," "Other Notepaper," "E.C. 10's," "Backs of Envelopes," etc. It is not so long since a meeting at B.M.A. House, in spite of suggestions to the contrary, was reminded that "the proper way for one doctor to communicate with another was by letter." Surely before we as family doctors or G.P.s attempt to improve our brethren we might attempt to put our own house in order.—I am, etc.,

Southampton. A. OAKLEY JOHN.

Eleven Vaginal Deliveries after Caesarean

SIR,—I was interested in the letter from Dr. E. N. Lamb on vaginal delivery after caesarean section (November 26, p. 1603), and especially in his statement that, "The usual management is to revert to caesarean delivery after two vaginal deliveries." I should be interested to know on what grounds he arrives at this conclusion, particularly as it follows immediately the remark that "nowhere is the answer to this particular problem given." Duckering[1] believes that the risk of rupture of the uterus is greatest during the first labour following caesarean section, succeeding labours being attended by a lesser risk of this complication, while Marshall,[2] in his important monograph on caesarean section, states that "the amount of interest displayed in the future of the scar is out of all proportion to its practical importance."

The regime suggested by Dr. Lamb in his concluding paragraph—"if intrauterine exploration of the scar immediately post-partum reveals no gross defect it is reasonable to advise a vaginal delivery in the next pregnancy"—which I advocated in 1953,[3] has been followed in this department for at least ten years. We set no arbitrary limit to the number of vaginal deliveries which may follow caesarean section, and we have no reason to believe that we are unorthodox in this—in this region at least.—I am, etc.,

Department of Obstetrics,
Southern General Hospital,
Glasgow S.W.1. DONALD F. BRUCE.

REFERENCES

1 Duckering, F. A., *Amer. J. Obstet. Gynec.*, 1946, **51**, 621.
2 Marshall, C. M., *Caesarean Section: Lower Segment Operation*. 1939. John Wright and Sons, Ltd., Bristol and London.
3 Bruce, D. F., *Glasgow med. J.*, 1953, **34**, 354.

SIR,—I was interested to see from Dr. E. Neville Lamb's letter (November 26, p. 1603) that in far-off New Zealand a Maori woman had achieved 12 full-time pregnancies within 17 years, after her first trial labour had ended in lower-segment caesarean section.

Her average rate of conception works out at eight months after the birth of each baby, and this in spite of her uterine scar. As it is fairly common practice in this country for mothers with uterine scars to be told

not to get pregnant under two years, and to present themselves at the nearest birth-control clinic because of the *danger* of getting pregnant and trying their scars to their limits, one wonders at the lack of faith our N.H.S. gynaecologists show in their scars.—I am, etc.,

Slough, Bucks. N. C. HYPHER.

John Lizars

SIR,—Among the writings of John Lizars is *A System of Anatomical Plates Accompanied with Descriptions and Physiological and Pathological Observations.*[1] The illustrations, engraved by his brother William, were drawn by himself and, under his supervision, by his brother. In the octavo volume accompanying the plates the text is enlivened by surgical observations from which it is apparent that by September, 1823, he had performed division of the maxillary division of the 5th nerve after it leaves the infra-orbital canal, for he gives precise instructions for performing the operation a few pages after describing those operations on the mandibular division which Dr. Simon Behrman described (December 3, p. 1665).

Lizars was not a man to mollify his opinions, and his admonition that "the knife should not be held as a pen, but with its cutting edge at right angles to the surface of the skin, so that the operator may sweep and not piddle with the scalpel," or his approving quotation of Dr. Pitcairn's remarks on his (Pitcairn's) exertions to set up an anatomical school in Edinburgh, "there is great opposition by the chief surgeons, who neither eat hay, nor suffer the oxen to eat it," though taken from his prefaces are not unrepresentative of the vigorous language in which the text is couched. So, too, when we read, "This very day I have operated on a gentleman from the contiguous county of England to that of the Worthy Mayor of Newcastle, for fistula in perineo, whose urethra was destroyed by one of the medical practitioners of the county attempting to introduce the catheter about three years ago," we have a forewarning of that lack of restraint in polemic which passed the bounds of tolerance in his remarks on Syme.

He wrote at a time when it was almost impossible to procure subjects for dissection, and used all his persuasive powers to ease the situation or at least influence those who could. In this action he occupies an honourable place among those who pioneered the way to the Anatomy Act, and Dr. Behrman does well to recall him to mind for us.—I am, etc.,

Royal Marsden Hospital, London S.W.3. ARNOLD LEVENE.

REFERENCE

1 Lizars, J., *A System of Anatomical Plates Accompanied with Descriptions and Physiological and Pathological Observations*, 1823–1826. Lizars, Edinburgh.

Vacuum Extractor in Obstetrics

SIR,—Many doctors following the correspondence of Mr. J. A. Chalmers and Mr. R. J. Fothergill (October 15, p. 1156) and Dr. E. W. Lillie (December 3, p. 1671) on the "Vacuum Extractor in Obstetrics" must be wondering what it is. One of these is on view in the Practice Equipment and Premises Room of the College of General Practitioners, where any doctor who cares may study it.—I am, etc.,

G. S. ADAMS,
Hon. Secretary, Practice Equipment and Premises Committee.

The College of General Practitioners,
41 Cadogan Gardens,
Sloane Square, London S.W.3.

An Abandoned Trial

SIR,—In view of the enthusiasm regarding the efficacy of mono-amine oxidase inhibitors in the treatment of depression, it is felt that our experience with one of them might be of general interest. Some time ago an experiment into the relative efficacy of nialamide and E.C.T. (modified by relaxant anaesthesia) was commenced. In the selection of patients every attempt was made to rule out of the series any who showed symptoms of anxiety accompanying the depression. Whilst the patients, who were referred, were divided into neurotic and psychotic conditions, the criteria of referral were the severity of the depression, which it was felt would respond to E.C.T. Each patient completed, before treatment by either nialamide or E.C.T., a series of questionary items purporting to measure different aspects of neurotic and psychotic depression.[1] The Wilcoxon non-parametric matched-pairs signed rank test[2] was used for the statistical analysis of therapeutic response.

After the drug had been tried for several months, the conclusion was reached that it was unethical to continue because evidence was lacking of the efficacy of nialamide in altering the depressive symptomatology, and the trial was therefore abandoned. Where response was towards improvement it was in no way comparable to E.C.T.—We are, etc.,

Winwick Hospital, Warrington, Lancs. P. M. O'FLANAGAN.
D. WALTON.

REFERENCES

1 Foulds, G. A., and Caine, T. M., *J. ment. Sci.*, 1959, **105**, 182.
2 Siegel, S., *Non-parametric Statistics for the Behavioural Sciences*, 1956. McGraw-Hill, London.

Alphabetical Relief of Pain

SIR,—The multiplicity of preparations now available for the relief of pain seems unbelievable. In effectiveness the range lies between morphine and aspirin, but alphabetically we may choose between aspirin and "zactirin."

The following list, already probably incomplete, seems worth recording and could well be included in an "Aids series" for students and doctors:

A: Aspirin, "alasil," "allonal," "antidol," "antoin," A.P.C., "anadin"
B: "Bropin," "barbasprin," "butazolidin," "bufferin"
C: Codeine, "caapi," "cafdis," "calpol," "Ce-K-Sal." "codis," "codalgin," "codasphen"
D: "Daprisal," "dexocodene," "D.F. 118," "doloxene," "disprin," "dolcin"
E: "Edrisal," "ekammon," "eneril," "equaprin"
F: "Febrilix," "fluscorbin"
G: "Gewodin," gelsemium
H: "Hypon," "heptalgin"
I: Ipecac and opium (Dover's), "irgapyrin"
K: "Kalmopyrin"
L: Levorphanol
M: Morphine, methadone, "mephosol"
N: "Narphen," "neurodyne," "naiodine," "nembudeine," "novalgin," "norflex"
O: Opium, "omnopon," "orgraine"
P: Pethidine, "panadol," "paynocil," "pethilorfan," phenacetin, "pipadone," pelfium, phenazone, "phalcin"
R: "Rasprin," "refagan"
S: "Solprin," "salimed," "saridone," "sinaxar"
T: "Tabalgin," "tercin"
V: "Valtorin," "veganin," "valgis," "vitasprin"
Z: "Zactirin."

It will be noted that preparations commencing with the letters: J, Q, U, W, X, and Y are missing, but if we count:

J: Jalap—as an ancient and maybe drastic cure for abdominal pain

U: *Uva ursi* (Bearberry) leaves—for the relief of colic due to diarrhoea

W: Wild cherry bark—which by means of hydrocyanic acid relieves a painful cough

Y: Yangonin—a resin from which is made "Extract Kavae Liq."—an intoxicating liquor giving anaesthesia akin to that produced by alcohol

and remember that "xaxa" was an old synonym for aspirin, then we are complete except for Q.

The question, therefore, must be whether our newly appointed querulous quartermaster, the Minister of Health, will decide that our quota is sufficient and put a quash on further production.—I am, etc.,

Pyle, Glamorgan. R. J. PHILLIPS.

Tooth Reimplantation

SIR,—Tonsillectomists run the risk of involuntarily extracting an incisor tooth at some time in their career. It so happens that this case report refers to the only tooth that I have so removed, but the interest is in the fact that after being out of the mouth for 10 minutes it was pushed back and remains fixed in position 16 months after the incident.

A European female child, aged 6, underwent operation for tonsillectomy and adenoidectomy on April 22, 1959. The tonsillectomy was uneventful, but just before the adenoids were removed there was some struggling and it was necessary to reinsert the Boyle-Davis gag. It was at this time that the upper left central permanent incisor was removed and retrieved. Adenoidectomy was then proceeded with and completed. After haemostasis, the patient was returned to the anaesthetic room. It was only at this point that the thought of trying to put the tooth back occurred, for a period of preoccupation had followed the extraction of the tooth. The tooth was recovered from the sluice room, wiped down, and pushed back into the socket, firmly but with no force.

Later that day when the mother called to see the child the affected tooth was still well down below the level of the adjacent teeth, and by no means firmly in position. When the child left hospital the following morning, little hope was entertained for the continued existence of the tooth *in situ*. The parents, in their understandable anxiety, took the child to the local dentist, who, however, said that nothing could be done, dentally speaking, to improve the future chances of the tooth.

The present position (November, 1960) is that the tooth is now firmly fixed in position. It is, however, still low and deviated to the left side. Radiographs show that the damaged tooth has a wide-open blunted apex.

A house-surgeon colleague boasted to me several years ago about a tooth, removed by trauma, that he had knocked back into place with the blow of a hammer. There was no follow up of this case and the hammer treatment sounds somewhat fierce, but we might have achieved a better position of the tooth if we had been more forceful in pushing or tapping it back. Another post-tonsillectomy case (also without follow up) treated by my dental colleague had a cap-splint constructed to hold the tooth back in position after its reinsertion. This sounds a reasonable idea and should have been applied to our case. I am informed that it is now too late for any form of orthodontic treatment to be effective. However, whatever we should or might have done, it has been most encouraging that the tooth has stayed put at all, and the case is reported to encourage anybody confronted by a similar unfortunate state of affairs to attempt immediate replacement, in the knowledge that there is a fair chance of success.

I wish to thank Dr. P. W. Dill-Russell, Director of Medical Services, Fiji, for permission to publish this case report.

—I am, etc.,

Lautoka Hospital.
Lautoka, Fiji. J. M. FOREMAN.

Dental Hygiene

SIR,—Whilst not presuming to speak for the dental profession I should like to comment on Mr. O. Gayer Morgan's letter (November 26, p. 1603) and his conclusions.

When he refers to the toothbrush as "septic" I assume he means very heavily contaminated with oral organisms, a condition which is inevitable, for the brush is used in the oral cavity which is, in his connotation of the word, also "septic," for it is also rich in organisms, becoming so some few hours after birth. In this respect the nylon brush harbours fewer organisms than the bristle type owing to the smoother surface of the nylon filament when compared with the rough surface of the bristle.

Toothbrushing has become necessary because of our methods of food preparation which result in a soft diet too easily masticated and with little detergent action on the teeth and oral tissues. As a result the jaw muscles get little to do, there is insufficient friction on the gingiva to maintain a proper degree of keratinization, and the soft food tends to lodge in and around the teeth. The toothbrush compensates to some extent for this by cleaning the teeth and by increasing the thickness of the keratinized layer of the gingiva. The gingival epithelium responds to friction much in the same way as the skin of the palm of the hand or the sole of the foot, with soreness and abrasion preceding an increase of keratinization. With an adequately keratinized gum-tissue the dangers of infection by the toothbrush are remote. An up-and-down or vertical motion is the method of choice, for it cleans interdentally, but not everyone seems capable of the manual dexterity to perform this properly, and with those a circular motion can be very effective. The important thing is to brush the gums as well as the teeth and to do it very vigorously with a hard brush.

Toothpastes are helpful in that they are detergent and pleasant to use, but a more effective though less elegant dentifrice is a mixture of equal parts of common salt and bicarbonate of soda. This is sufficiently abrasive to clean without scratching the enamel, breaks up mucin plaques, and promotes a salivary flow. Interdental sticks have their place in dental hygiene, especially in older people and in those cases where there has been a loss of the interdental papilla or where the anatomical arrangement of the teeth results in food impaction, by maintaining the interdental tissue in a healthy state.

Clinical observation and experimental investigation have not led me to the conclusion that the toothbrush should be regarded as a danger to oral health but the contrary. Of course it should be treated with reasonable care by being well rinsed and allowed to dry in the air after use and by being renewed at least every two months. If man were to return to a primitive state and to a diet of nuts, roots, leaves, raw meat, and fish, I am sure a toothbrush would be unnecessary; indeed

he would have no choice. But so long as man prefers sugar and spice and all things nice the toothbrush becomes a necessity, but he is left with the choice whether to use it or not.—I am, etc.,

London W.1. GEORGE A. COWAN.

SIR,—I should like to express my thanks to those who have answered my perhaps unduly provocative letter (November 26, p. 1603). Possibly I should have made a more humble approach in my quest for information, but I am sure it is true that few medical men have any accurate knowledge of the problems involved, and yet they are questions which are frequently cropping up and are expected to be knowledgeable and helpful. We are now very fully informed and I for one am duly grateful.—I am, etc.,

London W.1. O. GAYER MORGAN.

, This correspondence is now closed.—ED., *B.M.J.*

No Interview

SIR,—From time to time one hears complaints of the poor academic attainments of medical students. Is this now a thing of the past? A girl of 18 recently applied for a place at one of the London teaching hospitals. Her application was turned down without interview in the following terms: "Dear Madam,—Our vacancies for 1961 have now been filled, so I regret to tell you that you will not be called up for interview. It is fully appreciated that your academic record is good, but there were many others who were even better. Yours truly . . ."

The academic record in question was as follows: Eleven "O" level passes, ten at over 70% marks; four "A" level passes, two at grade I, one at grade II, and one at grade III. There may, of course, have been insufficient medical background. Only one grandparent was qualified. Both parents and an uncle are qualified.

I hope you will allow me to sign myself just

"PUZZLED."

Anthology of Graces

SIR,—I am compiling a book on grace said at meal-times. I would be grateful if any of your readers would send me any they know, and particularly any which are said at annual or other functions and which have a special bearing on their profession.—I am, etc.,

Channel View,
The Downs,
St. Nicholas, Cardiff. CHARLES F. SHEPHERD.

POINTS FROM LETTERS

Natural Gas

Dr. S. UA CONCHUBHAIR (Gaillimh, Eire) writes: While agreeing with the rest of what Dr. A. E. Mourant (November 26, p. 1597) has to say about natural gas and town-gas, I take issue with him on two points. He describes the natural gas, which in one case he identifies as butane, as "almost harmless." Perhaps he will tell us what he means by this. Does he mean that it is respirable and will support life, that if it leaks into my bedroom and fills it while I sleep it will not kill me? He refers to "calor gas," advertisements for which a few years ago stated that it was not poisonous. It appears that I must not have been alone in writing to the distributors to contest this statement, which they attempted to support by claiming that it had only an anaesthetic effect but which they have sinced ceased to publish.

Obituary

D. W. ROY, M.B., B.Ch., F.R.C.S., F.R.C.O.G.

Mr. D. W. Roy, consulting obstetric surgeon to St. George's Hospital, died at York on December 9, aged 79.

Donald Whatley Roy was born at Appleton Roebuck, Yorkshire, on May 22, 1881, the son of the Rev. James Roy. From St. Peter's School he went on to Sydney Sussex College, Cambridge, where he was an exhibitioner and scholar. Having taken first-class honours in both parts of the Natural Sciences Tripos, he won a university scholarship to St. George's Hospital, London. He qualified in 1906, winning the Brodie prize for clinical surgery, graduated M.B., B.Ch. in 1907, and took the F.R.C.S. in 1909. After qualification he held a notable series of resident hospital appointments, being house-physician, house-surgeon, and obstetric registrar and tutor at St. George's, house-physician and registrar at the General Lying-in Hospital and Samaritan Free Hospital, and senior resident medical officer at the Royal Free Hospital.

During the early part of the first world war he served in the Grand Fleet as a surgeon in the R.N.V.R., and from 1917 to 1918 he was a temporary major in the R.A.M.C., serving with a surgical division at the Northampton War Hospital.

Joining the staff of St. George's Hospital in 1919 as assistant obstetric surgeon, he became in the course of years consulting obstetric surgeon to the hospital, physician to the General Lying-in Hospital, and surgeon to the Samaritan Hospital for Women, and he was also in private practice. He was a member of the Board of Advanced Studies of London University, to which he was senior examiner in obstetrics and gynaecology, and he also examined for Cambridge University, the Society of Apothecaries, and the Conjoint Board. He was elected a Foundation Fellow of the Royal College of Gynaecology in 1929. Having been secretary and vice-president of the Section of Obstetrics and Gynaecology of the Royal Society of Medicine, he was vice-president of the corresponding Section at the Annual Meeting of the British Medical Association in Eastbourne in 1931.

Mr. Roy, who retired from active practice some years ago, is survived by his widow, two sons, and one daughter.

Mr. C. M. GWILLIM writes: Dr. Roy retired in 1938. I worked under him as resident and registrar from 1923. During the whole of that time he was handicapped by severe illness, which he faced with great fortitude. Perhaps it was the background of the Yorkshire vicarage—all his life was devotion to duty and extreme conscientious care. In spite of his physical disabilities, time, work, and fatigue did not matter. Naturally his patients were devoted to him, for he would make it his personal business to do for them things which others left to their juniors. He had a quick, shrewd, intelligent mind and a sense of humour which, in spite of everything, insisted on breaking through. His Cambridge academic record was first class and in obstetrics and gynaecology he was in many things far ahead of his time. His understanding of the anatomy of prolapse and his technique of breech delivery were modern. He devoted much time to teaching. Only the misfortune of ill-health prevented him making a great mark in our specialty.

R. L. GALLOWAY, M.B., Ch.B., F.R.C.S.Ed.

The death of Mr. R. L. Galloway on December 3, at the age of 65, has robbed British surgery of one of its most capable exponents. In recent years circumstances limited the use of his skill, but the numerous young surgeons he trained and the countless patients he treated will be saddened by his death.

Robert Lightbody Galloway was born in Edinburgh on March 3, 1895. He attended Daniel Stewart's College, and from his earliest days was remarkably skilful with his hands. Perhaps the prospect of long academic studies deterred him at first, for he spent some time in an engineering works after leaving school. But he really wanted to be a surgeon, and so he took up his studies in Edinburgh. After graduating M.B., Ch.B. in 1919, he held resident posts at the Edinburgh Royal Infirmary under Alexander Miles and Professor Caird. He then became personal assistant to Sir Harold Stiles at Chalmer's Hospital, Edinburgh, and from him quickly learnt his exquisite technique. A short period of general practice in Manchester followed, but he returned to surgery as resident surgical officer at the Manchester Royal Infirmary and at the Salford Royal Hospital, where he had a great reputation as a brilliant and dexterous surgeon. He took the F.R.C.S. Edinburgh in 1925.

In 1925 Galloway was appointed surgeon to the North Middlesex Hospital by the Edmonton Board of Guardians, a unique appointment in those days. In this extremely busy hospital he performed an enormous number of operations, and was constantly on call for emergencies. He built up the hospital's fine surgical reputation. When the second world war came he moved to Chase Farm Schools, and was instrumental in converting this large institution, originally an orphanage, and later an old folks home, into a complete general hospital staffed by the Emergency Medical Service. Much of the conversion to theatres and wards was done under his supervision. Those London Hospital students who worked in his wards saw a master surgeon at work, though they had to go elsewhere for the more academic aspects of surgery. Throughout the war Galloway kept Chase Farm Hospital, with around 700 beds, running smoothly, although often under difficult conditions.

Galloway was at heart a bedside surgeon, and, though he would have preferred to stay at Chase Farm Hospital when the war ended, he was persuaded by the Middlesex County Council to become medical director of the West Middlesex Hospital at Isleworth. There he used his organizing ability to bring this old sprawling hospital up to modern standards, but he continued to practise surgery and had wards at the near-by South Middlesex Hospital.

Galloway was a surgeon of rare ability who always impressed his assistants by knowing exactly what to do. He gave no appearance of hurry, yet the clock showed that he was a speedy operator. Interested in patients and not simply in technique, the human touch in surgery counted much with him. A kind and likable man, he never bore malice. The only criticism of him by his colleagues has been that he kept his light under a bushel and did not publish the results of his work. Few surgeons have had his vast experience, and once, when he had been persuaded to speak at an important meeting, some found his figures hard to believe.

Outside surgery Galloway had many interests. A superb craftsman, he has left examples of his work with clay and silver. He made and repaired surgical instruments in his own workshop. He never lost his interest in engineering, and was an expert and enthusiastic motor-cyclist and one of the stars of this sport. He contributed greatly to the success of several of the international six-day trials, and was a tower of strength to the British Autocycle Union.

At almost the end of his active career he was stricken with Parkinson's disease, a sad affliction for a man whose hands had meant so much. But he bore his burdens cheerfully, and turned his interest to books and conversation. The hope that modern surgery would bring back the joy of using his hands was not fulfilled. The sympathies of all his friends in many parts of the world go out to his widow, son, and daughter.—C. A. B.

J. M. D. writes from Enfield: "Robbie" Galloway—or "Galla"—came to the North Middlesex Hospital as surgeon 35 years ago. Those of us who were medical officers there found it difficult to believe that this young and unassuming man had the experience that he very quietly asserted he had. But we soon found that he had an impressive flair for diagnosis, an unerring judgment, and a technique which was quite exceptional. He was an indefatigable worker. His operating days were long and arduous. We who assisted him (in relays), or gave his anaesthetics, were often tired, but his last operation, frequently in the "wee sma' hours," was as quietly and as scrupulously performed as his first of the morning.

For twenty years he operated in this district and became an institution and a legend. He was loved alike by his patients and colleagues. The latter were frequently distressed by the innate modesty which prevented him from publishing much valuable work. The thought of such self-advertisement was repugnant to him. But his letters to the G.P. were models. He wrote about persons—not cases—and managed to convey the impression that the whole affair had been a "combined operation" between the G.P., the patient, and himself, with the patient as the most important person of all.

In his outside interests he was a remarkable man. He had a prodigious memory. What he saw he remembered in accurate detail; what he read or heard he never forgot. He was as much at home inside a motor engine as he was inside an abdomen. He modelled exquisitely in clay, he drew and painted with great skill. The design and craftsmanship of the silver tea service he made would not have disgraced Benvenuto Cellini himself. The disabling illness which struck him within sight of his retirement was a cruel blow, for he had hoped to do so much in the leisure he had so well earned.

He was singularly happy in his married life, with a charming wife, a daughter, and a son who practises medicine in Canada. He was devoted to them, and they, understandably, were devoted to him. We who were privileged to enjoy their friendship (and "Robbie's" skill) over so many years send them our deepest sympathy.

A colleague writes: Mr. R. L. Galloway was appointed medical director of the West Middlesex Hospital in January, 1946, during the opening phases of the post-war development in medical services. He immediately assumed direction of the expansion of the hospital, a process which was expedited by the advent of the National Health Service. It is not too much to say that the present prestige which the hospital enjoys is largely due to the industry, enthusiasm, and skill which Mr. Galloway put into the necessary planning and organization during these years. His advice was largely followed in the building of new operating theatres and the new out-patient department in 1951—the first large-scale post-war hospital construction in the country: these stand to-day as testimony to his ability and foresight.

When Mr. Galloway assumed the duties of an administrator he did not relinquish his love of surgery and he remained in general surgical practice until shortly before his retirement in March, 1960. Although he was mainly known as an abdominal surgeon, remarkable for his technique and operating speed, he remained until the end a general surgeon and avoided over-specialization.

He did little to indulge in his favourite sport of motor-cycle racing after joining the staff of the hospital, but he put his knowledge of engineering to good use, and his happiest hours were perhaps spent working on his lathe. He regularly serviced all surgical instruments throughout the hospital and in this way he must have saved the Health Service not inconsiderable sums of money.

Mr. Galloway was a great friend of his junior medical staff, who will always be grateful to him for guiding the

formation of a medical mess, and for his unceasing attempts to improve the residents' living conditions. He was a man one could always approach with a personal problem and be assured of getting a sympathetic hearing and receiving sound advice. He never attempted to achieve self-importance, but instead always remembered his own early days and gave unselfishly from his experience to help others. The affection that was given him sprang sincerely from the heart, and his presence as a friend will be sadly missed.

C. L. BALF, B.M., B.Ch., M.R.C.P., D.C.H.

Dr. C. L. Balf, who for the last five years had practised as a paediatrician in Kamloops, British Columbia, died there on October 14 at the age of 39.

Charles Lawson Balf was born on October 21, 1921. From Manchester Grammar School he won an open State scholarship to Merton College, Oxford. Completing his clinical training at the Radcliffe Infirmary, he graduated B.M., B.Ch. in 1945, took the D.C.H. in 1946, and the M.R.C.P. in 1947. After holding the post of house-physician at Newcastle Royal Infirmary he decided to specialize in paediatrics and became resident paediatrician at the Simpson Memorial Maternity Pavilion of the Edinburgh Royal Infirmary. Later he was elected to the George Guthrie Fellowship in Child Health at Edinburgh, becoming senior paediatric registrar at the Edinburgh northern group of hospitals and clinical tutor in the department of child health in the University of Edinburgh. During this period of his career he was the joint author of several papers which were published in this journal.

Five years ago Dr. Balf emigrated with his family to British Columbia, joining a clinic at Kamloops as paediatrician. He enjoyed his life there; both he and his wife took an active part in local affairs, and he became a keen fisherman. Last year he was a guest speaker at a regional medical conference.

His wife, Mary Birch, was a fellow student at Oxford, and she survives him, together with a son and two daughters.

Dr. T. T. S. INGRAM writes: The delayed news of the death of Charles Balf must have shocked and distressed all his many friends, colleagues, and patients in this country. They will remember with gratitude the brilliance of his mind, his capacity for friendship, and his gentleness. He had an encyclopaedic knowledge of paediatrics, but the impression of rather bookish learning that people often obtained when they first met him was deceptive. He was a brilliant diagnostician and had a deep appreciation of the psychological and social aspects of disease in childhood. These qualities were particularly evident in his work for the Scottish Council for the Care of Spastics at Westerlea School in Edinburgh. His understanding of the problems faced by the chronically handicapped child and his family earned him the absolute trust and affection of parents and the admiration of the staff. He was happier as a teacher at the bedside or in the clinic than when lecturing formally. But his skill in carrying out and demonstrating methods of examination is still remembered by his students, and his clinical teaching was vivid and exciting.

He was a born inquirer. Accepted ideas about children and their diseases existed only to be challenged and tested. The originality and penetration of his thought made him a most exciting and sought-after colleague whenever research was planned. He often complained of his inability to follow his own research projects to their logical conclusion, yet he seemed quite unaware of the extent to which other people's work was based on his ideas and how much they owed to his practical help.

His interests were not confined to paediatrics. He could talk with wide knowledge about many subjects. He read widely and remembered what he read. The breadth of his knowledge, the originality of his thought, his modesty and kindness, and his liking for people made him a most wonderful friend. He will be sadly missed by many people who will feel the deepest sympathy with his wife and family in their tragic loss.

W. BRODIE MOORE, M.B., Ch.B., D.P.H.

Dr. W. Brodie Moore, until recently medical officer of health of Maidenhead and the East Berkshire united sanitary district, died in Maidenhead Hospital on November 27, aged 65.

Born in Ayrshire, William Brodie Moore studied medicine at Glasgow, graduating M.B., Ch.B. in 1919. Before this he had spent four years as a probationer surgeon in a destroyer when serving in the Royal Navy during the first world war. After demobilization he became a general practitioner, working in mining districts, but he decided it was his duty to devote himself to preventive rather than curative medicine, and after a period of study in Newcastle he took the D.P.H. in 1927.

He then became medical officer of health at Brierley Hill, near Wolverhampton, and assistant medical officer with the Staffordshire County Council. Eight years later he took a similar appointment at High Wycombe, and came to Maidenhead in 1944 as medical officer of health to the East Berks united sanitary districts. This appointment entailed working for a number of different local authorities, which he managed admirably.

His personal charm and modesty, and his devotion to duty, won him admiration from all his employing authorities, although during the immediate post-war years his fight for better housing for overcrowded families often placed him in the heat of controversy. He was physician-superintendent of Maidenhead Isolation Hospital for almost the whole of his period in Maidenhead, retiring from this position in 1958. In this capacity he had charge of large numbers of patients passing through his hands, and was called upon to take the heavy responsibility for the poliomyelitis cases in the East Berkshire area extending far beyond Maidenhead, Slough, and Windsor. No public official in East Berks enjoyed a higher reputation, for he worked with devotion and success in the field of preventive medicine.

He made a major contribution to the health of the district in his efforts to reduce the causes of tuberculous infection by tackling this disease on all fronts—cleanliness, housing, early diagnosis, and diet. The progress made by his department—he was too modest to claim much credit for himself—is shown by the sharp decline in the official figures for this disease in East Berks.

Dr. Brodie Moore had been seriously ill for a few weeks after a period of ill-health which did not impair his ability to carry out his duties till his retirement shortly before his death. He is survived by his widow, two daughters, and a son, who is a pathologist in the R.A.F.

Dr. PHILIP H. WILLCOX writes: Dr. Brodie Moore was best known to his medical colleagues by reason of his position as medical superintendent of the Maidenhead Isolation Hospital from 1944 to 1958. I first came to know him in 1947 during the severe outbreak of poliomyelitis, when I gave him help over the diagnosis and treatment of many cases passing through his hands; and in subsequent years I had ample opportunity of observing his excellent qualities as a physician whose work was notable for his close attention to detailed observation, his unruffled courtesy, his manner of never seeming to be worried, and his cheerful attitude to patients.

He will be long remembered not only for his kindness and co-operation with general practitioners, who entrusted some of their most difficult cases to his care in hospital, but also with gratitude by numerous patients recovered from poliomyelitis and other infectious diseases from a wide area of Berkshire, Bucks, and Surrey, many of whom still

speak of him with affection. There are few M.O.H.s in this country with experience and knowledge of fevers equal to his. His past experience in general practice in his earlier years helped him much in this respect, for, being also conscious of his own limitations, he always sought help from consultant colleagues when necessity arose.

During his years at Maidenhead he saw many changes in the trend of infectious diseases in hospital—the conquest of diphtheria, the decline in poliomyelitis, and the diminishing severity of scarlet fever, measles, and whooping-cough. In recent years he had become interested in cancer progress and the methods whereby earlier diagnosis could be achieved by careful education of the public.

He had been looking forward to the enjoyment of further work in his garden during his retirement, but instead of this, having to face an illness of increasing severity, he did so with the greatest courage, and even cheerfulness, which all who knew him well have admired. The Windsor group of hospitals have lost one of their most outstanding specialists and many professional colleagues one of their best friends, who was always easily approachable and ready with sound advice during times of anxiety. To his widow, his son, and his two daughters our deep sympathy is extended.

D. H. SARAFIAN, M.R.C.S., L.R.C.P.

Dr. D. H. Sarafian, who had been in general practice in Chipping Sodbury since 1926, died there suddenly on November 29 at the age of 66.

Dirtad Haig Sarafian, who was of Armenian stock, was born in Turkey in 1894. He first came into contact with British prisoners of war when as a conscript in the Turkish Army he served in military hospitals during the Gallipoli campaign. All his sympathies were with his patients and what they had fought for, so that when Constantinople was occupied by Allied Forces he became a medical officer in the 82nd General Base Hospital of the British Army of the Black Sea. When he was free to resume his civilian medical career he came to Britain.

He studied at the Middlesex Hospital and qualified in 1923. It was in this year that he first came to Chipping Sodbury as assistant to Alfred Grace, the nephew of the great "W.G." During this time his affection for Gloucestershire and its people was established, and after two years as a ship surgeon he returned in 1926 as partner and successor to Dr. Grace.

In Chipping Sodbury he practised his art for 34 years, building up a deep and lasting reputation not only as a skilful obstetrician and diagnostician but as the truly pastoral G.P.—the kindly friend and adviser. This good doctor, an exile from his own country, succeeded in achieving a perfect fusion and understanding with the people of Gloucestershire among whom he worked; and his sudden death has brought deep sadness and sense of personal loss into many humble homes. His medical colleagues will remember the man and his work with the greatest affection and respect.

He leaves a widow and two sons, one of whom has almost completed his training at the Middlesex Hospital, and to them we offer our sincere sympathy.—J. M. N.

D. C. MONRO, C.B., C.B.E., M.B., Ch.B., F.R.C.S.Ed.

The obituary of Major-General D. C. Monro was published in the *Journal* of December 17 (p. 1810).

Major-General R. E. BARNSLEY writes: May I add a short tribute to the memory of Major-General Monro? For many thousands of us it seems almost impossible to think of the R.A.M.C. without "Jock," for he was the beau-ideal of the Army surgeon. Outstanding in his professional work, he was immensely popular with all ranks of the Corps and throughout the whole Army as well as among his civilian colleagues. It has fallen to my lot to be concerned in the training of young soldiers for over 30 years, and I served with him in many stations at home and overseas. Many memories come crowding in—of the intense and kindly interest he took in all who worked with him in the theatre and wards, and this not only in their technical work but also in their general progress and well-being in the Army. After a close friendship of some 40 years I cannot recall his ever having done or said anything mean or paltry, and those of us who have sat with him on various charitable committees will always remember his wise counsel and wholehearted sympathy with his comrades in distress.

D. C. B. writes: Major-General D. C. ("Jock") Monro was a human link of vital importance in the chain of surgical experience which fortunately for us joined the 1914–18 and the 1939–45 wars. The surgical lessons of 1914–18 were fully recorded and there for all to read in the official *History* and were to be found in many other sources as well, but in the heat and scurry of the opening stages of war history is often not read at all or its passages are misconstrued. We were fortunate to have in him one of a number of thoughtful surgeons who recalled from personal experience the lessons learned in the bitter school of 1914–18, and to have him in the right place to play a decisive part in adapting these and other lessons to the new conditions of 1939–45. He was particularly well qualified by his personal gifts for the role of harnessing the enthusiasm, devotion, and skill of his wonderful team of surgeons to the service of surgery in the field. I cannot, unfortunately, speak personally of this period, but it was no surprise to me to learn after the war had ended of his triumphs in the Middle East and later as the head of the Army surgical services in London.

He was one of the most widely known and popular surgeons in the Commonwealth, but I like to recall him as a friend of very long standing, kind and considerate to his juniors, courteous and generous to his colleagues. He was one of the best companions one could possibly have in any situation, and not very long before he died I spent a fascinating afternoon with him, to be regaled with stories from his experiences in all corners of the globe. His recollections and stories of student life and personalities in Edinburgh, of adventures at sea, of the first war, of India, and of the second war poured out, and when he talked of war his details were precise and his comments on events and personalities pungent and to the point. I wish he had himself written of the two wars; the material was there, and he could have recorded and fixed in his inimitable style for those who follow on the lessons that have had to be so painfully re-learned in each of our wars. In the last few years he suffered a number of illnesses, and more than once he had, in his own words, "taken a look over the brink" at what lies beyond, but had come back cheerful, active, and unafraid—to the joy of his many friends. He had great happiness in his wife and their small adopted daughter, who will miss him grievously. So will the vast company of his friends, who have cause to be grateful for having known him.

R. R. SIMPSON, M.B., Ch.B., F.R.C.S., F.R.C.S.Ed.

The obituary of Mr. R. R. Simpson was published in the *Journal* of December 10 (p. 1740).

W. N. R. writes: I first met Mr. Simpson when I went to Hull 11 years ago, and for the following decade it was my privilege to be one of his junior colleagues. He did not suffer fools gladly and was a hard taskmaster, but he had a large heart and a fine spirit which was receptive to new ideas. As an operator he was deft and speedy, and as a diagnostician he was superb. He was a shrewd counsellor and a loyal friend. For his support, for his wise and unselfish advice, and for his encouragement, those of us who worked with him will always owe him a debt of gratitude. It was his philosophy that difficulties were made to be overcome, and with his indomitable spirit he could never spare himself, much to the concern of his friends. The courage with which he faced the inevitable during his latter years was a constant and inspiring example to all of us who were privileged to know him well.

Medical Notes in Parliament

HUMAN TISSUE BILL

[FROM OUR PARLIAMENTARY CORRESPONDENT]

The repeal of the Corneal Grafting Act, 1952, is the least important part of the Human Tissue Bill, yet it typifies the whole background and purpose of this measure—to extend and clarify the law as it affects developments and advances in surgery. Its main object is to make it clear that, under the conditions it specifies, parts of a human body may lawfully be removed after death and used for therapeutic purposes or for medical education or research, and in this way to facilitate, by the removal of any limitation or uncertainty, the full application of new discoveries and skills through which the surgeon can employ human material for the relief or repair of damaged organs.

To this end, it is provided in Clause 1 that a person lawfully in possession of a body after death may authorize the removal of any part that the deceased person has in writing, or orally in the presence of two witnesses, requested should be used for medical purposes; or do so if, after reasonable inquiry, he has no reason to believe that the deceased person had expressed any objection to his body being so dealt with, or that the spouse or any surviving relative objected. Subsection (4) requires that no such removal shall be effected except by a fully registered medical practitioner, who must have satisfied himself by personal examination that life is extinct; and subsection (5) requires the coroner's consent in any case where there is reason to believe that there may be an inquest or that a post-mortem examination may be required. Since the Bill applies to Scotland (and to Northern Ireland), it is also stipulated that no authorization for removal is to be given if the procurator fiscal has objected. For a body lying in a hospital, nursing-home, or other institution, any authority under Clause 1 may be given on behalf of the person having the control or management by an officer designated for that purpose.

Post-mortem Examinations

Clause 2 places the existing practice of carrying out necropsies on a firm legal basis. It declares that the Anatomy Act, 1832—apart from post-mortem examinations directed or requested by a coroner or other legal authority—shall not be construed as applying to any post-mortem examination carried out for the purpose of establishing or confirming the causes of death or of investigating the existence or nature of abnormal conditions. No post-mortem examination is to be carried out otherwise than by or in accordance with the instructions of a fully registered medical practitioner; and, unless directed by a coroner or other authority, none shall be carried out without the authority of the person lawfully in charge of the body, and provided that there are no known objections on the part of the deceased person during his lifetime or the surviving spouse or relative. Clause 3 amends Section 13 of the Anatomy Act so as to enable bodies which have been used for anatomical examination under that Act to be lawfully cremated as an alternative to burial.

The Bill is a Government measure presented on December 8 by the Minister of Health and the Attorney General. The text was published the following day.*

QUESTIONS IN THE COMMONS

Mental Health Act in Scotland

Mr. HECTOR HUGHES (Aberdeen, North, Lab.) asked the Secretary of State for Scotland on December 6 what steps he had taken, or proposed to take, to implement the provisions of the Mental Health (Scotland) Act.

Mr. J. S. MACLAY replied that he intended that the Mental Health (Scotland) Act should be brought into operation by stages. The first stage would be to repeal the existing Lunacy Acts to the extent necessary to allow informal admission of patients to mental hospitals, in the same way as patients were admitted to general hospitals. The second stage would be to bring into operation Part II of the Act dealing with local authority services. He had already issued to local health authorities a statutory direction which imposed on them a duty to make arrangements for the purpose of the prevention of mental disorder and the care and aftercare of persons who were or had been suffering from mental disorder. He had also informed them that he would be calling on them to submit their proposals for mental health services, once he had received the advice on this subject of the Standing Advisory Committee on local authority services of the Scottish Health Services Council. The final stage would be to bring into operation the major part of the Act, dealing with the establishment of the Mental Welfare Commission, the procedure for patients who had to be compulsorily detained, and other matters. Introduction of this part of the Act involved consultations and the preparation of explanatory material for all those concerned with its operation, which must necessarily take some time.

Increase of Venereal Disease

Dr. DONALD JOHNSON (Carlisle, Con.) asked the Minister of Health on December 12 what steps he was taking to counteract the increased incidence of venereal disease amongst young people. Mr. ENOCH POWELL told him that local health authorities, hospitals, and general practitioners were reminded last year of their responsibility to co-operate in efforts to reduce the incidence of venereal disease generally, but "I am not satisfied that we yet understand sufficiently the significance or causes of the increase among young people, and I am considering how these can best be investigated."

Dr. JOHNSON asked the Minister to agree that this was an extremely serious problem owing to the new drug-resistant strains of infection that were about. While moral obligations in these days were unfortunately rather discounted, was it not within the Minister's scope at least to emphasize the virtues of personal cleanliness, which had lapsed in so many instances at the same time as other virtues? Mr. POWELL said he was not sure that moral obligations came within the scope of the Ministry. But he was sure that all those concerned understood the importance of emphasizing the right rules on all those with whom they came in contact.

New Royal College of Physicians

The MINISTER OF HOUSING AND LOCAL GOVERNMENT, questioned about his approval for the proposed new building for the Royal College of Physicians in Regent's Park, stated that this proposal had been referred to him by the London County Council because it constituted a departure from the approved development plan, in which this area was allocated for residential use. It involved the demolition of Someries House, which was originally designed by Nash as an adult orphanage, but little remained of his design: it had been extensively altered, and was now used as Government offices. In 1946 the Gorrell Committee reported that this building could and should be demolished. This view was accepted by the Crown Estate Commissioners, who decided to choose a skilled developer, advised by an architect acceptable to them, to redevelop the site in harmony with the surrounding Nash buildings and terraces.

The scheme of redevelopment, he continued, had been prepared by Messrs. Denys Lasdun and Partners for the Royal College of Physicians. The Royal Fine Art Commission said that they were well satisfied with the design: they felt that it would be acceptable as a neighbour to the Regency buildings which were to be preserved. The Crown Estate Commissioners had given their consent to the

*The text of the Bill is obtainable from Her Majesty's Stationery Office, London, price 6d. net.

plans. It was intended that all the trees on the western boundary facing Regent's Park should be retained. The St. Pancras Borough Council had no objection, subject to questions of access, and the London County Council were disposed to grant planning permission. Then he added that, before he authorized them to do so, he had arranged for a small model of the building and its setting to be exhibited to M.P.s for a week, so that they might have a chance to see the design for this important proposed building and its relationship to the Nash terraces.

Admission to Hospital

Mr. R. KELLEY (Don Valley, Lab.) asked the Minister of Health if, in order to equalize the period of waiting for admittance to certain hospitals, he would consider withdrawing the privilege that patients who consulted doctors privately had in being passed to the Health Service for investigation and treatment. Mr. POWELL replied "No," but if Mr. Kelley had evidence that a private consultation had secured earlier admission regardless of the relative urgency of the case he would be glad to look into it.

Mr. KELLEY said there was widespread evidence in his area that certain people, after private consultations with specialists, had been admitted earlier than they had been told admission would be available to them under the Health Service. There was an opinion that there were two classes of patients—those who could afford to pay the entrance fee to hospital, and those who had to wait. Mr. POWELL: If you will give me the opportunity of examining the basis of that opinion I will gladly do so. Mr. KELLEY: I will.

Hospital Capital Spending

Mr. H. BOYDEN (Bishop Auckland, Lab.) asked what amount of under-spending the Minister anticipated in the capital programme of hospital authorities in this financial year. Mr. POWELL stated that returns earlier in the year showed some under-spending, but hospital boards were authorized to undertake additional works. He could not anticipate the final out-turn. Mr. BOYDEN thought it deplorable that, when the Government set out at last to improve the hospital service and increase the amount of building, almost before it started they should be caught by under-spending. Mr. POWELL: I am anxious to spend if possible every penny of my capital estimate.

Reviews of Assistantships

Mr. L. PAVITT (Willesden, West, Lab.) asked how often the Minister required local medical committees to undertake a periodical review of assistantships in general practice; and what were the dates on which such reviews had been undertaken by the Middlesex Local Medical Committee. Mr. POWELL: Normally every two years. A committee of the Middlesex Executive Council which included members of the local medical committee had reviewed consents in October, 1957, June, 1959, and October, 1960. Mr. PAVITT welcomed the diligence of the Middlesex Committee, described abuse of the system of assistantships as "the nearest thing to slave labour," and asked the Minister to tighten up the general machinery for review. Mr. POWELL repeated that executive councils ought to carry out a review at least every two years.

Chiropody Services

Mr. J. WATTS (Manchester, Moss Side, Con.) asked the Minister whether, when giving his approval to schemes submitted to him under Section 28 of the National Health Service Act, 1946, by local authorities for chiropody services in their areas, he would make it a condition of his approval that existing chiropodists' private surgeries should not be excluded from such schemes, in so far as these related to service to persons over 65 years of age and to expectant mothers, both of which services were free. Miss EDITH PITT, Parliamentary Secretary, said "No," but most of the schemes approved provided for using the services of chiropodists in their own surgeries. There was power to charge in all cases.

Mr. WATTS described the present system as inconvenient to beneficiaries, who were not allowed free choice of practitioner, and unjust to chiropodists, who had to pay rates to the authorities competing with them. Miss PITT disagreed. There was still free choice for the patient. Since the local authorities met the cost of the services in the clinics they provided, it was right that they should have discretion in how they provided the services. Lord BALNIEL (Hertford, Con.) said that some local authorities based their chiropody services on their clinics to the exclusion of private practice and voluntary services, which was a cause of concern to the Institute of Chiropodists. Would the Parliamentary Secretary consider issuing model schemes for the use of local authorities? Miss PITT said it was for the local authorities to decide how they would operate the service. There was nothing to prevent their using chiropodists in their own clinics as distinct from using the chiropodists' own premises.

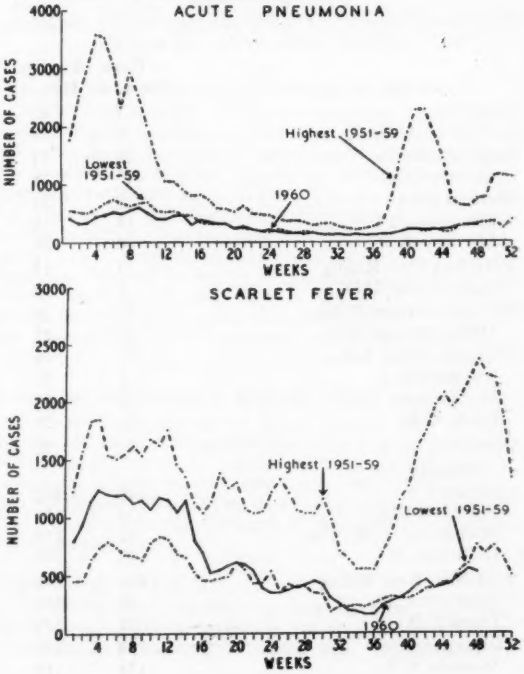
Rheumatism and Arthritis

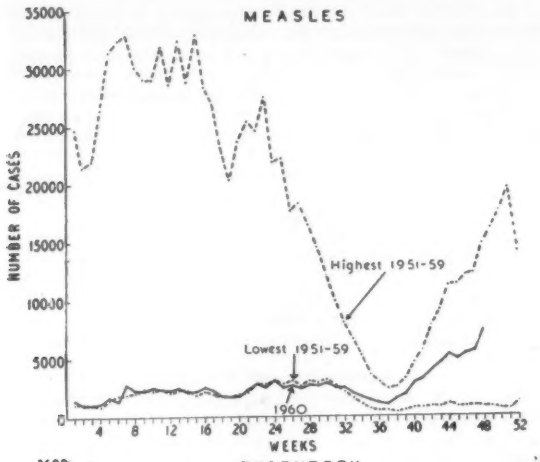
Mr. R. W. SORENSEN (Leyton, Lab.) asked the Minister what recent reports he had received in respect of the increase in rheumatism, arthritis, and similar complaints; and to what extent new treatments of this class of disease were ensuring definite alleviation or cure. Mr. POWELL said that he had received no evidence of increase in these diseases, though the rising average age of the population might justify a presumption. He was informed that no outstanding new treatment had become available during the last few years.

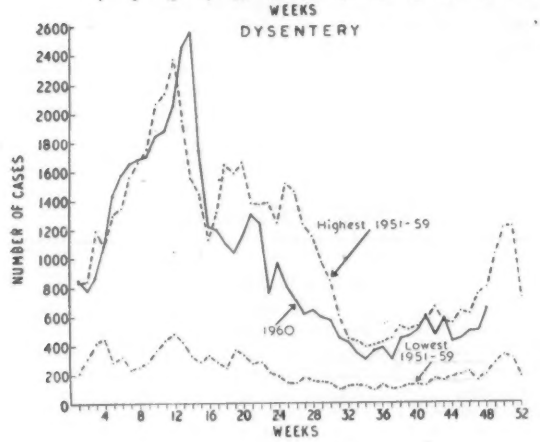
Vital Statistics

Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1951–9 are shown thus - - - - - -, the figures for 1960 thus ———. Except for the curves showing notifications in 1960, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.







Infectious Diseases

Areas where numbers of notifications were high in the latest two weeks for which figures are available.

	Week Ending Nov. 26	Dec. 3
Dysentery		
Cheshire	7	**41**
Hoylake U.D.	0	**32**
Nottinghamshire	31	**34**
Carlton U.D.	15	**15**
Warwickshire	19	**53**
Birmingham C.B.	14	**18**
Meriden R.B.	0	**26**
Yorkshire East Riding	5	**13**
Haltemprice U.D.	0	**12**
Yorkshire North Riding	10	**26**
Middlesbrough C.B.	10	**25**
Yorkshire West Riding	75	**99**
Bradford C.B.	8	**23**
Huddersfield C.B.	12	**19**
Leeds C.B.	27	**26**
Glasgow	112	**94**
Measles		
Lancashire	1,647	**1,902**
Liverpool C.B.	229	**221**
Manchester C.B.	67	**127**
Oldham C.B.	143	**151**
Yorkshire West Riding	488	**798**
Bradford C.B.	98	**195**
Leeds C.B.	63	**125**
Glamorganshire	258	**233**
Swansea C.B.	136	**110**

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **December 3** (No. 48) and corresponding week 1959.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1960 Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	1959 Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	3	3	2	0	1	5	4	4	0	1
Dysentery	646	50	136	4	13	723	96	153	7	9
Encephalitis, acute	1	0		0		1	0		0	
Enteric fever:										
Typhoid	0	0	0	0		3	1	0	0	7
Paratyphoid	7	1	0	1		1	0	3(B)	0	2(B)
Food-poisoning	144	25	8	2		190	39	7	1	
Infective enteritis or diarrhoea under 2 years				15	40				11	24
Measles*	7,234	400	197	37	114	1,110	26	22	13	69
Meningococcal infection	16	3	9	0	1	26	4	6	0	
Ophthalmia neonatorum	34	2	2	0		20	0	4	0	
Pneumonia†	273	25	183	1	2	305	15	210	5	1
Poliomyelitis, acute:										
Paralytic	12	4	0	0		11	3	0	0	4
Non-paralytic	1	0	0			2	0	1		
Puerperal fever§	173	26	13	0	1	156	19	9	1	1
Scarlet fever	536	37	70	18	19	1,418	90	131	28	21
Tuberculosis:										
Respiratory	381	57	58	8		430	50	75	10	
Non-respiratory	50	6	14	4		50	9	8	5	
Whooping-cough	1,096	73	86	4	67	739	53	187	7	87

DEATHS	1960 Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	1959 Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0	0	0	0	0	0	0	0
Dysentery	1	0		0		0	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	10	0	1	0	0	10	0	1	0	1
Influenza	15	0	2	0	2	19	2	0	0	1
Measles		0	0	0	0		0	0	0	0
Meningococcal infection		0	0				1	0		
Pneumonia	521	38	25	22	7	518	35	20	28	6
Poliomyelitis, acute	1	0		0	0	3	0		0	0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	87	7	11	1	3	87	5	3	4	3
Non-respiratory		0	1	1	0		0	1	0	0
Whooping-cough	0	0	0	0	0	0	0	0	0	0
Deaths 0–1 year	332	24	28	7	14	294	28	22	10	9
Deaths (excluding stillbirths)	10,359	806	633	157	177	9,945	785	549	174	167
LIVE BIRTHS	14,768	1253	988	255	420	12,877	1092	870	228	356
STILLBIRTHS	293	26	17			258	23	17		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Cambridge University Salaries

The council of the Senate of Cambridge University has agreed to the General Board's recommendation that a Grace should be submitted at Congregation on January 28 which says, in effect, that the stipends payable from January 1 will be in accordance with the University's choice by a ballot to be held on February 2 and 3. The main point at issue is, as described in a leading article in the *Journal* (November 26, p. 1579), whether or not differential salary scales should be abolished, and the choice which the University may exercise lies between a scale of stipends which may be expected to be either (*a*) the same for non-medical, preclinical, and clinical staff, or (*b*) the same for non-medical, and preclinical, but different, and higher, for clinical staff, or (*c*) different for non-medical, preclinical, and clinical staff.

Queen Mary's Hospital, Roehampton

The administration of Queen Mary's Hospital, Roehampton, is to be transferred from the Ministry of Health to the Board of Governors of Westminster Hospital. The separate identity of Queen Mary's will be maintained and war pensioners will continue to have the same priority as at present. The Limb-fitting Centre will continue to be administered by the Ministry of Health. The number of war-pensioner patients at Queen Mary's has gradually diminished, and at the end of November this year there were 370 beds available, of which 118 were occupied by war-pensioner patients as against 190 by National Health Service patients.

Dental Auxiliaries' New Training School

The Minister of Health, Mr. ENOCH POWELL, has opened a new training school for dental auxiliaries at New Cross, London. He said that in his own county of Staffordshire the most recent report showed that only 21% of children entering school had completely sound teeth compared with 39% in 1947, and that we had the international reputation of being a nation of false-teeth wearers. He believed that the new school for 60 students, rising to 120, and experimental for at least three years, marked the beginning of a new attack upon the nation's deplorable standards of dental health.

Scottish Children's Teeth

An interim report by the Scottish Standing Committee on Dental Health Education, *Our Children's Teeth*, says that "the root cause of the increase in dental decay lies in the increased consumption of sweets, 'lollies,' fruit drinks, and biscuits between meals. . . ." At the age of 5 the typical Scottish child has seven of his 20 temporary teeth decayed, filled, or extracted. At 14, 12 out of 28 permanent teeth are affected. In 1958, 3,609 children in Scotland aged up to 16 had whole or partial National Health dentures—the highest number recorded and nearly twice as many as in 1954. The report stresses the need to improve oral hygiene and feeding habits, and says that children eat too few hard foods such as apples and carrots. (Department of Health for Scotland. Edinburgh: H.M.S.O., price 1s. 6d. net.)

Diet and Teeth

The General Dental Council has produced a film about diet and dental health called "Guilty or not Guilty," which has been partially financed by the Farmers Union, the Commonwealth Fruits Council, the British Egg Marketing Board, the National Milk Publicity Council, and the Flour Advisory Bureau. It can be borrowed free of charge from Science Services, 269 Kingston Road, Merton Park, London S.W.19. There is a waiting-list.

British Council

The British Council gives details in its *Annual Report 1959–60* of overseas visitors in the United Kingdom under Council auspices: of 6,040 visitors 1,052 were concerned with medicine. The visit to Rumania of Dr. E. A. CARMICHAEL, chairman of the Council's medical advisory panel, is noted as being the first Council-sponsored tour there for many years, and one of 70 such visits made to all parts of the world by specialists in the medical and para-medical field. The Council's policy on books and periodicals is described as placing more emphasis on scientific, technical, and medical textbooks.

Smallpox in Nyasaland

Dr. P. R. STEPHENS, the director of medical services in Nyasaland, has reported that since January 1, 1960, 604 cases of smallpox have been notified, and there have been 40 deaths. In the whole of 1959 there were 559 cases of smallpox and only 13 deaths. Mr. B. D. GOLDBERG, the Federal Minister of Health, has stated that recently the situation in Nyasaland has taken a definite turn for the worse, and that political intimidation was playing a major part in worsening the smallpox epidemic. In 1959, despite the emergency and the disturbances following it, 800,000 vaccinations were completed—an average of 66,000 per month—whereas in 1960, even with increased staff and much effort on the part of the Ministry of Health in the past six months, the average had been only 30,000 a month, an unsatisfactory figure in view of the mounting number of cases (*The Federation of Rhodesia and Nyasaland Newsletter*, 48/60, December 12). In the House of Lords on December 15, the EARL OF PERTH, Minister of State, Colonial Office, said in answer to a question that the epidemic of smallpox in Nyasaland had not subsided. In two instances where medical teams had been hindered by physical intimidation, the authorities had brought forward cases for trial: one had resulted in the conviction of offenders and the other was shortly to be heard (*The Times*, December 16). A letter on this subject appears on p. 1882 in this issue.

Society for Visiting Scientists

The DUKE OF EDINBURGH has consented to become patron of the Society for Visiting Scientists. The Society, which came into existence during the war, offers at its house, 5 Old Burlington Street, London W.1, a centre at which foreign and overseas scientists visiting the United Kingdom may meet informally with other visitors and with British scientists. Further information about the Society may be obtained from the Assistant Secretary, Miss E. SIMPSON, at the above address.

Christine Murrell Memorial Fellowship Award

The Medical Women's Federation invites applications from women medical practitioners who are registered in one of the countries of the British Commonwealth of Nations and are on the British *Medical Register* for the Christine Murrell Memorial Fellowship award (£150). The award will be made for research, or associated secretarial expenses, and equipment. It will be for one year and be renewable for one further year. Application forms may be obtained from the Secretary, Medical Women's Federation, Tavistock House North, Tavistock Square, London W.C.1, to whom they should be returned by April 30, accompanied by a plan of the proposed subject of research and the names of three referees.

Society for Psychosomatic Research Prize

Through the generosity of the Sir Halley Stewart Trust the Society for Psychosomatic Research is offering a prize of £50 in 1962 for the best paper reporting original observations on a psychosomatic theme studied in patients seen in general practice. The closing date for entries is December 1, 1961. Details from the Secretary of the Society, 96 Portland Place, London W.1.

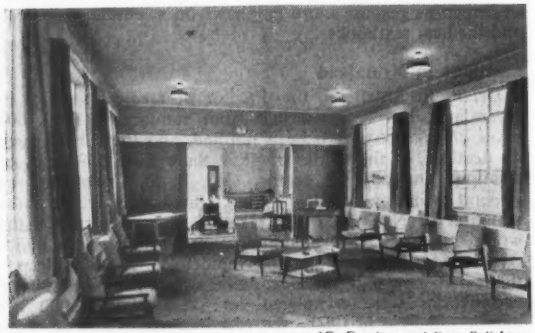
"Agressologie" Prize

The editors of *Agressologie* (see *Journal*, May 21, p. 1580) are offering a prize of 2,000 N.F. for an essay on a subject (experimental or clinical) concerned with "psycho-biologie

ou de pharmacologie appliquées aux effets de l'agression." Details may be had from *Agressologie*, 14 rue Drouot, Paris 9, France. The closing date is April 30.

Medical Staff Residence, Odstock Hospital

A new residence was recently opened for medical staff at Odstock Hospital, Salisbury.



[*F. Futcher and Son, Salisbury*

Lounge and dining-room at Odstock Hospital.

There are 17 bed-sitting-rooms in the residence, each with its own handbasin and built-in furniture ; serving these rooms are conveniently placed bathrooms, showerbaths, and toilets. There is a large lounge which is separated from the dining-room by sliding doors, and meals are served from a small service kitchen adjoining the dining-room. A library has been provided away from the living-room area so that medical staff can study without disturbance. The building stands on the hospital perimeter overlooking the Wiltshire countryside, and from some windows the spire of Salisbury Cathedral can be seen. Two flats have been built for married medical staff near the new residence. The cost of the whole scheme, including furnishings, was £35,000.

"No Smoking"

The Board of Management of Edinburgh Royal Infirmary is to enforce existing "No Smoking" notices in corridors, staircases, and out-patient departments. Consultants, along with their ward sisters, are being asked to allocate sections of their units for patients who want to smoke. Visitors are to be "discouraged" from smoking in the hospital. (*Glasgow Herald*, December 14.)

"Oxford English Dictionary Supplement"

The editor of the *Oxford English Dictionary Supplement* is seeking an earlier printed date than the one given in brackets for the following words. Communications should be addressed to the Editor, *Oxford English Dictionary Supplement*, 40 Walton Crescent, Oxford.

Ornithosis=psittacosis (1939), oxygen bottle (1941), oxygen mask (1930), oxygen tent (1933), paediatrician (1903), Pavlovian (1951), pep pill (1954), phenylketonuria (1938), polio (1931), pre-clinical (1930), pre-Freudian (1937).

In Brief

A bust of Sir ALEXANDER FLEMING has been unveiled in Eleftheria Square, Athens, which has been renamed Fleming Square in his honour.

Women's Institutes for patients in mental hospitals have been successfully established at Fulbourn Hospital, Cambridgeshire ; Deva Hospital, Chester ; Arden Hospital, Warwickshire ; and Tone Valley Hospital, Somerset.

People in the News

Mr. DEAN RUSK, president of the Rockefeller Foundation, has been chosen as the U.S.A.'s next Secretary of State.

Mr. N. L. SHELTON has been appointed Minister of Health and Social Security in New Zealand's new Government.

Dr. G. W. CORNER, For.Mem.R.S., historian of the Rockefeller Institute, New York, and director emeritus, department of embryology, Carnegie Institution of Washington, has been appointed executive officer of the American Philosophical Society, Philadelphia. He will retain a connexion with the Rockefeller Institute as visiting professor.

Dr. W. P. COCKSHOTT, University College Hospital, Ibadan, Nigeria, has been awarded a National Academy of Sciences–National Research Council grant for radiological research on behalf of the James Picker Foundation, U.S.A.

COMING EVENTS

British Occupational Hygiene Society.—Day meeting, "Health Physics," January 4, 10 a.m., London School of Hygiene, Keppel Street, London W.C.1. Details from Dr. J. S. MCLINTOCK, Medical Service, National Coal Board, Hobart House, London S.W.1.

British Institute of Radiology.—Annual Congress, April 26–28, Church House and Central Hall, London S.W.1. Applications to exhibit at scientific exhibition by January 7 to Dr. R. OLLERENSHAW, Department of Medical Illustration, Manchester Royal Infirmary, Manchester 13.

Institute of Diseases of Chest.—Clinical demonstrations, open to medical practitioners without fee, arranged by Dr. K. M. CITRON, Institute lecture-room (grounds of Brompton Hospital, Fulham Road, London S.W.3), Fridays, 5 p.m., January 13–March 24 inclusive.

British Association of Physical Medicine.—Annual meeting, April 21 (Royal National Orthopaedic Hospital, Stanmore), April 22 (Westminster Hospital). Abstracts of suggested papers or films by January 30 to Honorary Secretary, B.A.P.M., 47 Lincoln's Inn Fields, London W.C.2.

NEW ISSUES OF SPECIALIST JOURNALS

*The journals listed below are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London W.C.*1.

BRITISH JOURNAL OF OPHTHALMOLOGY

Intra-ocular Acrylic Lenses : 10 Years' Development. H. Ridley.
Results in 39 Bilateral Ridley Intra-ocular Implants. W. S. Reese.
A Plea for Lateral Orbitotomy. H. B. Stallard.
Choroideremia. J. K. Pameyer, P. J. Waardenburg, and H. E. Henkes.
Effects of Some Metabolic Inhibitors Upon the Formation of the Aqueous Humour in Rabbits. D. F. Cole.
Incidence of Glaucoma in Various Ethnic Groups in the Population of Israel. J. Landau and H. S. Halevi.
Hydroxyphenylbutazone (Tanderil) in the Treatment of Ocular Disease. L. E. J. Werner.
Clinical Trial of Chlorhexidine and Diaminodiphenylsulphone in Superficial Ocular Infections. P. A. Graham.
Scleromalacia Perforans. P. Sivasubramaniam and D. Mutucumarana.
Review.
Index for 1960.

Volume 44, No. 12. (Monthly; £6 annually. With *Ophthalmic Literature* and index, £9.)

OPHTHALMIC LITERATURE FOR 1960

Vol. XIV, No. 2 (607–1384). (Quarterly. £4 annually if taken separately.)

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Thursday, December 29

LONDON JEWISH HOSPITAL MEDICAL SOCIETY.—At Medical Society of London, 8.15 p.m., Dr. C. O. Carter: Advice to Parents on Genetic Risks.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Begg.—On December 10, 1960, at the Jersey Maternity Hospital, to Christine, wife of Dr. Douglas Begg, a sister for Andrew and Elizabeth —Patricia Ann.

DEATHS

Davar.—On November 15, 1960, at 35 Rebsch Street, Club Back Road, Byculla, Bombay, India, Rustom Ardeshir Davar, M.B., B.S., F.R.F.P.S., D.C.H., B.Hy., Lieutenant-Colonel, I.A.M.C.
Grant.—On November 15, 1960, at Durban, Natal, South Africa, William Gordon Grant, M.D., F.R.C.O.G., late of Johannesburg and recently of The Leeht, Bothas Hill, Natal, aged 87.
Hyman.—On November 29, 1960, in hospital, David Ephraim Hyman, M.R.C.S., L.R.C.P. of 13 Old Hall Road, Broughton Park, Salford, Lancs.
Lewis.—On November 28, 1960, Philip Cecil King Lewis, M.R.C.S., L.R.C.P., of Bromyard, Herefordshire.
McCartney.—On November 25, 1960, at Radcliffe Infirmary, Oxford, John McCartney, L.R.C.P.&S., L.R.F.P.S., of Prospect Place, Bampton, Oxford.
Mitchell.—On November 25, 1960, in hospital, William George Mitchell, M.B., B.Ch., of Gorsefield Cottage, Noctorum, Birkenhead.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Asthma in a Sooty Atmosphere

Q.—*An asthmatic girl aged 17½ is likely to qualify for university entrance, and the question arises whether the sooty atmosphere of an industrial area such as Birmingham or Liverpool would be harmful. Skin-tests four years ago showed sensitivity to feathers, house-dust, and grass pollen. During the past three years her attacks have decreased. The girl seems psychologically well adjusted for university life.*

A.—There is no reason to believe that a young girl leaving home to live in the sooty atmosphere of Birmingham or Liverpool would have more asthma there. If, as her skin-tests suggest, she is sensitive to feathers, house-dust, and grass pollen she will be somewhat less exposed to grass pollen in the summer, and it should not be difficult for her to avoid feathers and have a suitable bedroom. She should look after herself reasonably, avoiding so far as possible too many late nights and catching cold. Young people are not infrequently somewhat better when away at university than when at home.

Combined Tranquillizer and Anticholinergic

Q.—*Are there any advantages in combining a tranquillizer, such as trifluoperazine, with an anticholinergic agent, such as isopropamide?*

A.—Trifluoperazine is one of the phenothiazine group of tranquillizers which have attained a considerable reputation in the treatment of certain psychiatric disorders. Their usefulness in anxiety states, whether characterized by obsessional paranoid or phobic manifestations or by depression, and even in cases of paranoid schizophrenia, is now established. In these conditions there is no reason to suppose that the addition of an anticholinergic agent would enhance the therapeutic activity of trifluoperazine, although it is possible that isopropamide or some similar preparation might counteract the increased salivation which is sometimes a troublesome side-effect of treatment with the phenothiazine group. Because the chief therapeutic effect of trifluoperazine is to relieve anxiety, tenseness, and hyperactivity it has been suggested that it might prove a useful drug for the treatment of peptic ulcer, on the grounds that these symptoms are frequently present in ulcer patients and are thought by many to be aetiologically important. Anticholinergic agents such as belladonna, propantheline, isopropamide, and tricyclamol have long been used in the treatment of peptic ulcer in the belief that they diminish excessive motility in the gastro-intestinal tract and reduced gastric secretion. For the treatment of peptic ulcer and other so-called psychosomatic disorders of the gastro-intestinal tract the manufacturers have therefore produced a proprietary preparation which contains both trifluoperazine (1 mg.) and isopropamide (5 mg.) and it is presumably to this that the question refers.

It is claimed that the combined preparation controls the cause—i.e., the central nervous and emotional factors which may be responsible for peptic ulcer—by trifluoperazine, and the effect—i.e., the increased gastric secretion and the hypermotility which together are responsible for pain, nausea, and vomiting—by isopropamide. If the first of these claims were true then there would seem to be no need for the second drug. In a condition in which symptomatology is as variable as it is in peptic ulceration, and in which spontaneous relapses and remissions are known to occur frequently, one would be hesitant to accept such claims unless they were supported by evidence from a well-controlled clinical trial. It is well known that the majority of ulcer patients respond well to any new form of therapy when it is first prescribed, and for this reason the results of short-term studies, such as that of Arden,[1] cannot be considered adequate evidence that this new preparation has any advantages over older and well-tried remedies for the treatment of peptic ulcer. An additional point, and one which applies to many compound preparations, is that it is unlikely that the optimum dose of the tranquillizer and the anticholinergic drug will be the same for every patient, and the use of a combined preparation which contains the two drugs in fixed proportions does not allow the flexibility of dosage which is necessary for good treatment of the individual patient.

REFERENCE

[1] Arden, L. D., *J. roy. nav. med. Serv.*, 1960, **46**, 30.

Senile Vulvitis

Q.—*What is the treatment for recurrent vulvitis of two years' standing and causing intense irritation and insomnia in a woman aged 70? There is no glycosuria or vaginal discharge. Sedatives and the local application of cortisone lotion gave dramatic relief at first but are now losing their effect. Should stilboestrol be given, and in what dose?*

A.—"Vulvitis" is a term open to various interpretations. If it is here being used loosely to mean some sort of skin change associated with pruritus vulvae, then the possible causes are many, and, unless the cause is found, no treatment is likely to be satisfactory. Cortisone preparations do no more than prevent the skin reacting to whatever the offending agent may be. Oestrogens also are generally best avoided. They counteract senile atrophy of the vulval skin and improve its resistance to infection, but they rarely, if ever, cure pruritus due to any cause. They also have undesirable side-effects such as causing uterine bleeding.

The only satisfactory approach to a case of this kind is a complete investigation which aims to exclude conditions such as achlorhydria; avitaminosis; other deficiency states; anaemia of any type; hyperglycaemia; allergy to foodstuffs, drugs, clothing, and toilet preparations; trichomonas infection of the vagina; monilia infection of the vulva, vagina, and any other part of the body; tinea infection of the hands and feet; and any other skin disease present at other sites. Moreover, it may be necessary to carry out biopsy of the vulval skin if only to exclude malignant disease. An intra-epidermal cancer of the vulva presents none of the typical naked-eye appearances of malignancy and can resemble a patch of inflamed skin. The treatment is then determined by the findings.

Persistently Low Blood-pressure

Q.—*What may be the cause of a persistently low blood-pressure (systolic below 100 mm. Hg) of at least 15 years' standing in a woman aged 44 with a history of childhood rheumatic fever, but with no clinical evidence of cardiac lesion? All investigations yield normal results, but lassitude is pronounced. There are no menopausal symptoms.*

A.—The most likely cause of persistently low blood-pressure and pronounced lassitude is adrenal cortical insufficiency, but the long history of 15 or more years would seem to render this improbable unless some replacement therapy is being administered, or the deficiency is only partial. Hypotension may accompany serious chronic organic disease such as cancer or tuberculosis, but again the long history makes this unlikely. Orthostatic or postural hypotension, in which the blood-pressure falls dramatically on standing up and gives rise to syncope, is a possibility. Such hypotension is due to failure of normal compensatory vasoconstriction on standing so that blood pools in the lower extremities and leads to a fall in central venous pressure, cardiac output, and arterial pressure. It may complicate disorders of the nervous system, such as tabes dorsalis, diabetic neuropathy, or syringomyelia, or it may be

idiopathic and accompanied by anhidrosis and impotence. Orthostatic hypotension is much more common in males than females, and is due to a disturbance in function of the sympathetic venous system causing failure of vaso-constriction. Undue sensitivity of the carotid sinus may cause an abrupt fall in blood-pressure and bradycardia when the sinus is compressed, as in turning the neck suddenly, and fainting may occur.

Chronic hypotension and lassitude may be due to a very low cardiac output as a result of cardiac constriction (constrictive pericarditis) or of a severe obstructive valve lesion such as aortic stenosis, but the absence of any abnormal clinical signs in the cardiovascular system rules out these conditions. The ganglion-blocking drugs characteristically produce postural hypotension, but these were not available 15 years ago, and it is presumed that the patient is not taking these or other hypotensive drugs at the present time. Chronic salt-deficiency may cause hypotension, and salt-deficiency could arise from poor intake or excessive loss from vomiting (or to a lesser extent sweating), or from a salt-losing renal lesion. The last, however, would probably be associated with renal insufficiency and a normal or elevated blood-pressure.

Finally, it should be remembered that occasionally a low blood-pressure may occur in normal persons, and it is probable that this is the case in the patient quoted if clinical signs of disease are absent, no drugs are being taken, no food fads are being indulged in, and all investigations are negative. Lassitude is a non-specific symptom and may arise from psychogenic disturbance; it may be as unwise to tell a patient that the blood-pressure is unduly low as that it is unduly high. In the absence of the disorders quoted above, it can be said that the prognosis in a patient with a systolic blood-pressure of less than 100 mm. Hg is certainly better than that of a person with a pressure of over 200 mm. Hg.

Are Fat Babies Chesty ?

Q.—*It is said that fat babies are more subject to bronchitis than other children. The usual expression is: "Fat babies are inclined to be chesty." Is there any evidence to support this impression?*

A.—This is a very widespread belief, and it would seem reasonable to suppose that there was some basis for it. This might be an association between excessive carbohydrate intake and general care and exposure to infection. It might be that the fat baby tends to be more static and later in sitting up and consequently less well able to get rid of bronchial catarrh than his more lively and thinner brothers. This, however, is supposition and has no statistical basis. My own experience does not support the idea that at present there is any association between obesity in infancy and a tendency to bronchitis.

Ill-effects from Physiotherapeutic Waves

Q.—*Is it possible that a person working all day and every day in a hospital physiotherapy department might be affected in any way by "waves" from the apparatus?*

A.—The wavelengths of the electromagnetic spectrum used in a department of physical medicine are not dangerous to those who use them, and no reports of any ill-effects on those in their vicinity have ever been published.

Treatment of Ménière's Disease

Q.—*What treatment might give some relief in a case of Ménière's disease in a woman aged 60 who has had symptoms on and off for over 30 years?*

A.—The first thing in a suspected case of Ménière's disease is to find out which ear is affected and to what extent both balancing and hearing function have been damaged. When, as is usual, the disorder is limited to one side, and the hearing on that side is badly affected, then labyrinthectomy should be considered. This is not a serious procedure, but it does mean that the cochlear and vestibular function on that side are destroyed. However, when hearing is impaired or distorted on that side, its loss is no handicap. The noises may continue, but every patient submitted to this operation is grateful for the relief from the attacks.

Before this is done conservative treatment should be given a trial, the most successful form being a limited sodium and fluid intake. In about one-half the cases this keeps the attacks at bay if the patient can keep to the diet. This means no salt at the table, no added salt in the cooking, and no salty foods. In this way sodium intake can be kept down to ½ g. a day, thus discouraging fluid retention. Fluid intake rarely need be restricted below 3 pints (1.7 litres) per day. Drug treatment will not prevent attacks, but "avomine" or "stemetil" will tend to minimize their effects.

NOTES AND COMMENTS

Treatment of Obsessional Neurosis.—Dr. ELLIS STUNGO (London W.1) writes: I find "Any Questions ?" a most interesting and valuable feature of the *Journal*. For example, the information given on the use of oral contraceptives and ovarian function (November 19, p. 1537) would be widely appreciated. But was it wise to attempt to answer the question on the same page on the modern treatment of obsessional neurosis in a man aged 44 ? If, as your expert stated, obsessional neurosis is not a clear-cut entity and there is therefore no specific treatment, should not the questioner have been advised to read the subject in a modern textbook or refer his patient to hospital ? Obsessional neurosis merits a special article and no real service can be rendered to general practitioners by attempting to condense it. Nor do I consider it wise to mention a galaxy of drugs, some of which have been found useful in tension and depressive states, because, inevitably, a number of doctors might thereby be tempted to try some of them in a case for which they proved unsuitable. If "Any Questions ?" is to continue to play and discharge its useful role the advice offered should be precise, uncontroversial, and, as far as possible, capable of implementation by the questioner, if some action is indicated.

OUR EXPERT replies: Dr. Stungo's suggestions appear to miss some pertinent matters. Thus we might assume that a practitioner sending in a query has tried, and failed, to find the answer. Moreover, the question and answer will be read by other doctors. How many possess modern textbooks on medicine or on psychiatry ? Many general practitioners do not know that there is any treatment for obsessional or other neuroses. It is thought desirable—as has been done in this instance—to give an answer telling the doctor what he can do and at the same time mentioning that further treatment (leucotomy, etc.) is available should this be required. It would be impracticable, even if it were desirable, to send every obsessional patient to hospital merely because there is no specific treatment.

Dr. M. MULCAHY (Dublin) writes: I was impressed by the concise, clear-cut answer to the question: "What is the modern treatment of obsessional neurosis in a man aged 44 ? " in your "Any Questions ?" section of the *Journal* of November 19 (p. 1537).

Collected Articles from the "British Medical Journal"

The following books are available through booksellers or from the Publishing Manager, B.M.A. House. Prices, which include postage, are now the same for both inland and overseas.

Refresher Course for General Practitioners, Volume 3 (26s. 9d.).
Clinical Pathology in General Practice (22s. 3d.).
Any Questions?, Volume 3 (8s. 3d.).

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